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Modifiable Midlife Risk Factors for Late-Life Cognitive Impairment and Dementia

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Abstract

The baby boom generation is approaching the age of greatest risk for cognitive impairment and dementia. There is growing interest in strategies to modify the environment in midlife to increase the probability of maintaining cognitive health in late life. Several potentially modifiable risk factors have been studied in relation to cognitive impairment and dementia in late life, but methodological limitations of observational research have resulted in some inconsistencies across studies. The most promising strategies are maintaining cardiovascular health, engagement in mental, physical, and social activities, using alcohol in moderation, abstaining from tobacco use, and following a heart-healthy diet. Other factors that may influence cognitive health are occupational attainment, depression, personality, exposure to general anesthesia, head injury, postmenopausal hormone therapy, non-steroidal anti-inflammatory medications, and nutritional supplements such as antioxidants. Some long-term observational studies initiated in midlife or earlier, and some randomized controlled trials, have examined the effects of specific cognitive health promotion behaviors in midlife on the risk of cognitive impairment in late life. Overall, these studies provide limited support for risk reduction at this time. Recommendations and challenges for developing effective strategies to reduce the burden of cognitive impairment and dementia in the future are discussed.

Keywords

Lifestyle; Cognition; Alzheimer's disease; Epidemiology

INTRODUCTION

The population of older Americans continues to grow at an unprecedented rate [1]. A public health campaign, "The Healthy Brain Initiative: A National Public Health Road Map to Maintaining Cognitive Health" [2], spotlights the urgency to increase our understanding of what contributes to healthy brain aging. This call for action reflects estimates that the number of cases of Alzheimer's disease (AD), the most common cause of cognitive impairment and dementia in older adults [3], may quadruple in the next forty years if no effective therapeutic or preventative strategies are discovered [4]. Maintaining cognitive health in late life has important implications for overall well-being and independence, health services utilization and costs, long-term institutional care, and caregiver burden, as well as personal and societal resources [5].

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As the baby boom generation transitions into late adulthood during the next 20 years, the search is on for effective preventative strategies to reduce the prevalence of cognitive impairment and dementia in this age group. By definition, primary prevention of disease requires risk factors to be modified before the onset of disease. Neurodegenerative and cerebrovascular diseases are generally chronic, progressive conditions with pathology developing over years before symptoms and deficits are experienced The purpose of this review is to summarize existing evidence of *modifiable* risk factors associated with cognitive health that may be targeted to the baby boom generation, of whom 10 million are projected to develop AD [3]. Emphasis will be placed on prospective longitudinal studies, especially those assessing risk in midlife, and randomized controlled trials, except where only cross-sectional studies have been reported. Where evidence is available, potential mechanisms by which these factors may be involved in the causal pathway leading to cognitive impairment or dementia will be described. Finally, challenges, recommendations, and future directions for epidemiologic studies of cognitive impairment and dementia will be offered. This review is intended to encourage both researchers and clinicians to consider "moving back the bar" [6] to earlier points in the life course. The desired goal is to assess modifiable risk factors so as to target patients for preventative strategies in midlife, thus potentially reducing the burden of cognitive impairment and dementia in the subsequent decades.

CONSIDERATIONS IN THE STUDY OF MIDLIFE RISK FACTORS FOR COGNITIVE HEALTH IN LATE LIFE

Spectrum of Cognitive Change in Late Life

Three types of cognitive changes are recognized in late life: normative cognitive aging, cognitive impairment, and dementia [7]. While declines in cognitive functioning are not an inevitable part of aging, the majority of older adults experience some slowed speed of processing [8]. Other abilities such as memory, spatial ability, and reasoning also are more likely to decline with normal aging, whereas verbal abilities, information, and comprehension tend to show stability [9]. Several terms have been used to describe cognitive decline in normal aging including age-associated memory impairment (AAMI) [10], age-related cognitive decline [10], and aging-associated cognitive decline [11]. Mild cognitive impairment (MCI) [12] and cognitive impairment no dementia (CIND) [13] are considered intermediate states between normal cognitive aging and dementia where individuals experience cognitive deficits greater than expected for their age, but do not fulfill diagnostic criteria for dementia. Both MCI and CIND may be associated with a heightened risk of progression to dementia [14,15]; although there is an ongoing debate in the literature whether these entities merely represent early or incipient dementia rather than true risk states or factors [16]. Finally, dementia is a chronic syndrome characterized by acquired cognitive deficits in more than one cognitive domain, currently including memory, that are severe enough to affect daily (social and occupational) functioning, do not occur solely in the context of delirium, and cannot be fully accounted for by another mental disorder [17]. Alzheimer's disease is the most common subtype of dementia, followed by vascular dementia (VaD) and mixed dementias with both degenerative and vascular pathology. In the current review, we examine published evidence for all types of cognitive change in late life; mostly focusing on cognitive change beyond what is considered normal (hereafter referred to broadly as cognitive impairment and dementia).

Epidemiologic Definition of "Risk"

Epidemiologists use the term "risk" to describe the future probability of disease as a function of a particular exposure, at the population level. Risk is said to be increased or decreased in relation to the exposure, with decreased risk referred to as a protective effect. Risk is estimated from two basic types of analytic studies: observational studies (case-control and cohort) and experimental studies (randomized controlled trials (RCT)).

Observational studies gather naturalistic information in real-world settings on exposures and disease outcomes. The risk estimates calculated from observational studies include the odds ratio (case-control), risk ratio (cohort), and hazard ratio (cohort) and represent the degree of association between an exposure and disease outcome. They do not necessarily imply a direct causal relationship. The observed association should only be interpreted as a signal suggesting where there is an underlying mechanism to be explored. The exposure in question may indeed be in the causal pathway, or it may be a mediator or moderator of the effect of a different exposure, or even a confounder.

Experimental studies are conducted after there is sufficient evidence from observational studies to warrant randomizing individuals to a treatment (e.g. drug or behavioral intervention) or control condition. Randomized controlled trials are considered the gold standard since the researcher has control over the exposure of interest, potential confounding influences are minimized, there is generally high internal validity, and causal associations can often be tested [18].

Difficulties arise when the findings from observational studies are not replicated when tested in RCTs. Since the RCT is regarded as the gold standard, discrepancies between observational and interventional studies are often interpreted as proving the observational study to have been incorrect. However, the experimental intervention may have been undertaken with the wrong exposure; or the exposure may be in the causal pathway but not modifiable; or the timing and duration of the exposure may have been critical in determining whether it leads to disease and when it may be modifiable. Furthermore, mass media reports of population-level observational studies often lead the general public to believe that the findings apply to them at the individual level. For example, after reading a report that red wine consumption and cognitive activity were associated with lower risk of dementia, the reader may conclude that his drinking red wine or doing crossword puzzles will prevent him personally from developing cognitive impairment or dementia. A month later he may read about a different study conducted on a different population over a different period of time, in which wine consumption was not associated with risk of dementia. Thus, apparent discrepancies among observational studies, and also between observational and interventional studies, have tended to damage the credibility of observational research.

Genetic versus Environmental Risk Factors

It is now widely accepted that cognitive impairment and dementia are associated with both genetic and environmental risk factors. Genetic factors have been studied most in relation to AD risk, and have been reviewed by Ashford and Mortimer [19]. In the rare familial form of AD with onset before age 60 years of age, point mutations in the amyloid precursor protein (APP, chromosome 21), the presenilin 1 (PS1; chromosome 14), and the presenilin 2 (PS2, chromosome 1) genes cause autosomal dominant transmission of the disease. In non-familial AD, which constitutes at least 95% of cases, only the apolipoprotein E (APOE) gene on chromosome 19 has been identified as a major risk factor [20,21]. Possession of the ε4 allele of the APOE gene increases risk while the ε2 allele appears to be a protective factor [22]. Evidence is mixed as to whether APOE ε4 increases risk of cognitive impairment in people who do not develop dementia; however, the results of a meta-analysis suggest that APOE ε4 has a small, domain-specific (e.g. global cognitive functioning, episodic memory, and executive functioning), influence on normal cognitive aging [23]. Evidence from studies of early-life risk factors, family and twin studies, and other potential gene candidates, suggest that non-familial AD is mainly due to genetic factors which contribute to the pathological progression of disease, while gene-environment interactions are also important [19,24,25].

Thus, there is potentially strong genetic risk for cognitive impairment and dementia, but genetic factors are, of course, not modifiable at this time. Consequently, there is considerable interest

in environmental factors, some of which are modifiable, that may be associated with cognitive impairment and AD. Generally speaking, the environment is thought to explain the non-genetic risk for cognitive impairment and dementia by affecting the timing of clinical expression of symptoms [24,25,26] as opposed to their overall presence or absence of pathology. Higher environmental risk would contribute to earlier clinical expression or onset, while lower risk would lead to later clinical onset. Thus, "prevention" of cognitive impairment and dementia can be conceptualized as delaying the clinical expression and onset of diagnosable disease beyond the individual's lifetime.

The concept of brain reserve has been proposed to explain how modifiable risk factors affect the clinical expression of cognitive impairment and dementia [24,27]. Two types of brain reserve have been proposed: passive and active [28]. In the passive model of reserve, brain structure (neuron and synapse number or brain size) provide the basis for reserve, and consequently is determined primarily by genetics but may be influenced to some degree by environmental influences (e.g. nutrition). The active model of reserve, more commonly known as "cognitive" reserve, is concerned more with neural processing and synaptic organization than neuroanatomical differences. Neural processing and synaptic organization are more sensitive to environmental influences such as education and mental stimulation; therefore it is these changes that provide the greatest potential for increasing reserve [28]. Thus, by contributing to brain reserve, the modifiable factors under consideration may determine the difference in timing of onset of clinical symptoms between two individuals with similar brain pathology. In other words, if two individuals have the same degree of underlying brain pathology, the one with greater cognitive reserve may be able to compensate for it, and delay the onset of clinically significant symptoms and disabilities, longer than the one with lesser reserve.

Mortality

In studies of older adults, mortality can have an important and often neglected impact on study results. Any sample of older individuals represents a group of survivors, in the sense that they did not die at an earlier age. Several of the risk factors that have been studied in relation to cognitive impairment and dementia are also risk factors for mortality [29]. For example, individuals carrying the ε4 allele of the APOE gene are at elevated risk not only for Alzheimer's disease but for atherosclerotic heart disease, and may die from heart disease before they reach the age of risk for dementia. Similar patterns are observed with modifiable risk factors such as obesity where both overweight and obesity are associated with increased mortality in later life [30]. Stroke can lead to cognitive impairment and dementia, and can also cause death; in a population with high stroke mortality rates, the effect of stroke on increasing risk of cognitive impairment and dementia may be hard to observe. In addition, cognitive decline [31] and AD [32] themselves are associated with elevated mortality rates. This phenomenon, known as "competing risk," can appear to attenuate the effect of a risk factor /exposure on outcome.

Bias, Confounding, and Other Methodologic Issues

We have discussed above the impact of mortality on risk estimates. Mortality can also lead to biased samples. In cross-sectional studies, using prevalent cases of dementia, there is strong potential for a differential survivor bias. Here, fewer cases of dementia are observed than expected in the true population because more individuals at greater risk of dementia (compared to those at lesser risk of dementia) would have died before the study sample was drawn. Those with dementia are therefore under-represented in the sample as compared to the true population that the sample is supposed to represent. In longitudinal studies, bias due to participant attrition may obscure the findings where fewer observed exposed cases are followed than expected in the true population due to increased mortality. Hence, inconsistent findings across studies may be due to differential mortality rates and life expectancy in the populations that were studied,

or to researchers failing to appropriately adjust their analyses for data that were non-randomly missing because of death.

Other methodological challenges that can distort results include difficulties in precise measurement of exposures leading to potential misclassification bias, inadequate accounting for variation in the exposure or covariates over time, lack of or inadequate adjustment for potentially confounding factors, the exposure of interest being a proxy for the true etiologic risk factor, differences in the cognitive outcome and/or how it is defined, and insufficient statistical power [33]. Differences in the underlying population may also contribute to inconsistent findings since, for example, a sample of nuns and a sample of veterans may have different base rates of the exposures as well as of the outcomes, and may have different moderators and confounders (e.g. substance use, head trauma).

Life Course Approach to the Study of Cognitive Impairment and Dementia

Increasingly, experts in the field of cognitive aging and dementia research have been calling for a life course approach [6,34,35,36]. Life course epidemiology is defined as “the study of long term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life” [37]. This approach emphasizes both the temporal order of exposures and their interrelationships, including geneenvironment and environment-environment interactions. It allows a clearer distinction between cause and consequence, and allows the detection of changes over time in the relationship between the exposure and the disease. Under this model, researchers must begin to examine risk factors not merely a few years before clinical onset of disease, but decades earlier. Only then can they adequately study how these factors contribute to the initiation of brain changes associated with cognitive impairment or dementia, to their progression (positively or negatively), or their expression [6,35]. An exposure measured for the first time in late life, shortly before onset of clinical symptoms, and found to be associated with disease, may itself be the consequence of the same underlying pathological process that has caused the symptoms after progressing silently for decades. [38,39,40,41]. Thus, many of the findings from case-control studies, as well as short-duration cohort studies, may be explained by “reverse causality”. For example, as will be shown later, incipient brain disease may lead to low blood pressure making it seem that high blood pressure is protective against dementia, while studies of the association between midlife blood pressure and late-life cognitive impairment and dementia have revealed that high blood pressure increases risk. Or, incipient brain disease may lead individuals to curtail their mental activities well before symptoms appear, leading us to assume that lack of activity caused disease, or increased activity protected against disease. Thus, it is critical that we understand the directionality of associations when developing interventions.

Early-life Risk Factors

Midlife risk factors are not independent of early-life influences. An exhaustive review of early-life risk factors for AD has been published previously [42] and is beyond the scope of this article. Here, we provide only a brief overview of early-life risk factors in the context of a life course perspective of the relationship of midlife risk factors with cognitive impairment and dementia in late life.

The risk for cognitive impairment and dementia may begin as early as *in utero*. Fetal undernutrition [43], low birth weight [44], and not being breast-fed [45] may have long term direct negative consequences for cognitive performance. They may also lead to increased susceptibility to other chronic diseases [46], specifically vascular disease and its risk factors (e.g. hyperinsulinemia, diabetes, atherosclerosis, hypertension, cholesterol, and serum lipids) that have been linked to dementia and AD. In early childhood, a greater number of siblings [47] and lower birth order [48] may influence cognitive development and subsequent risk of

late-life cognitive impairment and dementia through a "resource dilution" effect [49]. Lower socioeconomic conditions may affect other early-life factors including nutrition, environmental stimulation, and access to education, which may retard brain development and body growth, intelligence, and later cognitive performance. Other markers of low socioeconomic conditions in early life such as father's employment as an unskilled laborer [50] and urban residence [47] have also been found to be associated with increased risk of dementia. Finally, several studies using anthropometric indices such as maximal adult height [51], knee height [52], arm [52] and leg length [53], and head circumference [54,55,56,57] as markers for early-life environment have shown inverse associations with cognitive ability, dementia, and AD in late life.

The most researched early-life risk factor for cognitive impairment and dementia is educational attainment. For most, a significant portion of early life is spent attending school with some variation by cohort and culture. Across studies, lower educational attainment is consistently found to increase the risk of cognitive impairment [58,59,60,61] and dementia [62,63,64,65, 66]; although this finding has not been replicated in all studies [67]. There are several potential explanations for how education is associated with cognitive impairment and dementia including: 1) education produces a detection bias where ceiling effects on cognitive tests prevent those with higher education from meeting diagnostic criteria for impairment despite loss of abilities; 2) education is a surrogate for other early-life factors such as socioeconomic status (SES), nutrition, and IQ, and influences risk factors in later life such as occupation, physical health, and health habits; and 3) education increases cognitive reserve [27] by offering long-term potentiation-induced neuroprotection [68].

Thus, there is accumulating evidence that early-life environment plays a role in cognitive health in late life and has potential downstream effects on adult socioeconomic status, physical and mental health, and health-related behaviors (e.g. engagement in stimulating activities, alcohol and tobacco use, and diet/nutrition) in midlife. However, middle-aged adults are not in a position to change their early-life risk factors, and these are the individuals who in very large numbers are approaching the age of greatest risk for cognitive impairment and dementia. Consequently, if the burden of cognitive impairment and dementia is to be reduced in the coming decades, more research needs to focus on modifiable risk factors in midlife.

MIDLIFE RISK FACTORS

Occupation

Strong evidence that education is associated with late-life cognitive health has spurred interest in a similar association between occupation and cognitive impairment and dementia. Studies of the association between primary lifetime occupation suggest that lower occupational status (e.g. manual labor, trade, farmer), based on occupational classifications, may be associated with poorer cognitive performance [69] and increased risk of dementia [69,70] and AD [63, 66,71]. Conversely, complex occupations with higher mental or intellectual demands compared to physical activity [72,73,74] or that primarily involve working with people [75] and things (i.e. "coordinating" data, "persuading" people, and "feeding/offbearing" things) [76] is associated with greater benefit to cognitive performance in late life and a reduced risk of dementia.

The link between occupation and cognitive impairment and dementia is complex, with proposed mechanisms (mediators) including occupational exposures, intellectual stimulation, and occupation itself serving as a proxy for other risk factors. It has been suggested that those whose primary occupation is considered low-status have a greater likelihood of adverse occupational exposures [71,77] that may contribute to damage to the nervous system. The "use it or lose it" hypothesis [78,79] posits that mental exercise maintains brain health by increasing

brain and cognitive reserve; therefore, occupations with greater intellectual demands should benefit the cognitive system and preserve cognitive health with aging. One study of AD patients found that greater previous occupational demand was associated with relatively greater deficits in cerebral blood flow in the parietal regions. This finding was interpreted as suggesting that individuals with more demanding occupations were able to compensate longer for AD-associated brain pathology before showing accelerated decline [80]. Finally, occupational attainment in adulthood is closely linked to educational attainment, intelligence, socioeconomic status, and other health behaviors (e.g. tobacco and alcohol consumption) that are themselves associated with cognitive impairment and dementia. Studies that have attempted to tease apart the role of occupation from these factors have thus far been inconclusive, although the association has been shown to be independent of education and intelligence [73]. It is also possible that occupational pursuits themselves are affected by the effects on cognition of very early neuropathology.

Vascular Conditions

What is good for heart health may also be good for brain health since there are similar risk factors for heart disease and dementia. Cardiovascular disease is the leading cause of death among adults [81]. A great deal of effort has already been made to understand ways to reduce its prevalence through the prevention and management of its risk factors, including high blood pressure, high cholesterol level, diabetes mellitus, and obesity. In general, evidence for the associations between these conditions and dementia suggests a nonlinear (U- or J-shaped) association, with stronger risk estimates in midlife compared to late-life [82]. This highlights the importance of the timing of the assessment for understanding what levels actually represent risk, rather than markers, of preclinical disease. It also suggests that the timing of the exposure itself may be critical in influencing risk of future disease.

Blood Pressure—As of 2002, approximately 30% of U.S. adults over the age of 20 years were either diagnosed with hypertension or were taking blood pressure-lowering medications, with another 28% considered “prehypertensive”. In addition, it is estimated that upwards of 90% of middle–aged adults will develop high blood pressure at some point during their lifetime [83]. Overall, evidence in support of an association between blood pressure and dementia suggests that it varies by age, where high blood pressure in midlife is associated with mild cognitive impairment [84] and increased risk of dementia [85,86,87,88,89], but in late life is associated with a reduced risk of dementia [90,91]. Further, it has been shown that blood pressure begins to decrease approximately 3 years before the diagnosis of dementia [92] and continues to decline in AD [93,94] with increasing severity [90]. The best interpretation of these findings is that high blood pressure in midlife increases the risk of cognitive impairment and dementia in late life, whereas late-life low blood pressure’s association with dementia is a consequence of the accelerated aging process and underlying neuropathology.

Potential mechanisms that may explain the association between midlife blood pressure and late-life cognition include high or variable midlife systolic blood pressure leading to atherosclerosis [95], white matter lesions (indicative of ischemia) [96], as well as increased neuritic plaques and tangles in the neocortex and hippocampus [97], and hippocampal [98, 99] and amygdalar [98] atrophy. Each of these can negatively affect cognitive functioning in late life. Low blood pressure in late life may be associated with an increased risk of cognitive impairment and dementia due to neurodegenerative changes in the brain that result in cerebral hypoperfusion [100].

It is as yet unclear whether or not antihypertensive drug treatment can attenuate the link between midlife high blood pressure and increased risk of late-life cognitive disorders. Differences between studies in the age of participants, comorbidities, level of blood pressure control, type

of anti-hypertensive treatment, and type of cognitive assessment may explain inconsistencies in study results [101]. An early cross-sectional report indicated that antihypertensive medication reduced the risk of cognitive impairment in older adults with a trend toward protection against dementia and AD [102]. Findings from two prospective studies using data from the Honolulu-Asia Aging Study (HAAS) reported that midlife antihypertensive use was associated with less hippocampal atrophy [99] and that longer duration of use was associated with a reduced risk of dementia [103]. A systematic review of randomized placebo-controlled trials revealed that blood pressure lowering treatments do not improve performance on all cognitive domains [101]. This study, however, included middle-aged to older adults and is not specific to midlife antihypertensive use. Another systematic review examining the findings of randomized placebo-controlled trials of antihypertensive use and dementia found that of the four trials, two reported a benefit from antihypertensive therapy while two did not [104]. Future studies should examine in more detail the duration of antihypertensive use, type and dosage, and level of blood pressure control.

Cholesterol—The association of cholesterol level with cognitive impairment and dementia has been investigated in several epidemiologic studies. The findings from these studies are inconsistent, with the best explanation being that the timing of cholesterol measurement in relation to the time of dementia onset affects the association that is found. Similar to blood pressure and other vascular risk factors, high total cholesterol in midlife may be associated with an increased risk of cognitive impairment [84,105,106] and dementia [86,107] and AD [87,88,108,109], while high late-life cholesterol may not affect risk [110,111,112,113] or be associated with lower risk [114]. Additionally, studies have shown that cholesterol levels begin to decline before the onset of dementia and that greater decline between mid- and late-life is associated with more severe cognitive impairment in late life [105]. Here, as with blood pressure, it seems that a nonlinear association exists where high cholesterol in midlife is a risk factor and low cholesterol in late life may be a consequence of aging [115] and/or neuropathological changes associated with dementia [109,114].

The role of cholesterol in the pathology of dementia seems intuitively linked with the APOE ε4 allele discussed earlier. Compared to the ε2 and ε3 isoforms of the protein, ε4 is associated with poorer transport and clearance of serum cholesterol [116] which can result in elevated serum cholesterol at mid and late life [89]. High total cholesterol may then lead to atherosclerosis, which impairs blood flow to the brain, and acceleration of AD neurodegeneration [117] by affecting the metabolism of beta amyloid (Aβ) protein which is seen in excess in AD brains and is the primary component of plaques [118,119,120]. The reduced risk of dementia in late life with higher late-life cholesterol may be related to cholesterol's role in neuronal plasticity [121] or to its antioxidant properties [122], or, alternatively, to a general wasting and loss of body mass associated with AD [123].

If high cholesterol is a true risk factor for cognitive impairment and dementia, then the use of lipid-lowering medications (i.e. HMG Co-A reductase inhibitors or "statins") would be expected to be associated with reduced risk. Early evidence from cross-sectional studies supported a lower probability of dementia in those who had used statins [124,125]. This finding could result from statins offering protection against dementia, or from physicians being less aggressive about treating hyperlipidemia in dementia patients [125]. The latter explanation is plausible since the early cross-sectional findings were not replicated in two subsequent clinical trials [126,127] or prospective studies [128,129,130,131] with the exception of two studies that found statin use reduced the risk of incident cognitive impairment and dementia [132,133]. It has also been suggested that statins might play an anti-inflammatory role [134] in reducing the risk of AD. Whether cholesterol-lowering medications are a viable strategy to prevent or delay cognitive impairment and dementia will have to be determined by longer prospective studies beginning in midlife. Additionally, many of the same questions raised for antihypertensive

medications also need to be addressed such as the timing and duration of use, type and dosage, and level of cholesterol control.

Diabetes Mellitus—Type II diabetes mellitus (non-insulin dependent) currently affects approximately 8% of the total U.S. population, with the prevalence rising with age to approximately 23% of those 60 years and older [135]. With the exception of findings from Curb and colleagues [136], the presence of diabetes in midlife has been shown to be associated with an increased risk for MCI [137], all types of dementia [86,138,139], AD [85], and vascular dementia [85] in late life. A recent population-based case-control study examining the association between diabetes mellitus and MCI suggests that it may not be the presence of diabetes mellitus per se, but earlier onset, longer duration, and greater severity of diabetes mellitus that increases the risk of cognitive dysfunction [140]. Another study found that impaired insulin secretion, glucose intolerance, and insulin resistance also were all associated with higher risk of any dementia and cognitive impairment up to 35 years later [141]. Hyperinsulinemia also has been shown to be associated with poorer cognitive performance and with cognitive decline in middle-aged adults [142] and older adults [143]. The same associations generally hold or are even stronger in studies of late-life diabetes [82], in contrast to the nonlinear associations observed with other vascular conditions.

The exact mechanism that explains the link between diabetes and cognitive impairment and dementia is not well understood and likely involves several inter-related processes. The three most common pathways involve vascular, metabolic, and inflammatory/oxidative processes [144]. Diabetes leads to diseases of the vasculature, including the cerebrovasculature. This effect may lead to brain ischemia contributing to the development of subcortical white matter lesions, silent infarcts, and atrophy, which have been shown to be more prevalent and severe in the brains of diabetic patients in MRI studies [145]. Insulin itself may be involved in cognitive impairment and dementia where “cerebral insulin-resistance” may affect neuromodulation in brain areas important for cognition. Metabolism of Aβ and tau [146,147], the primary proteins of the hallmark plaques and tangles in AD brains, also may be directly affected by insulin levels, and contribute to elevated cognitive impairment and dementia risk. Diabetes is also associated with elevated inflammatory factors, e.g. C-reactive protein, interleukin-6, and tumor-necrosis factor-α, and with higher levels of reactive oxygen species, which also have been shown to influence the risk of AD [144]. Animal studies investigating other potential mechanisms, such as the role of advanced glycation endproducts [148], are beyond the scope of this review.

Limited evidence exists regarding whether improving glycemic control among diabetics decreases the risk of cognitive impairment and dementia. One observational study found that treated diabetics showed less cognitive decline compared to untreated diabetics [149], and the UK Prospective Diabetes Study, a randomized trial of treated versus untreated older diabetics, found better performance on a cognitive screening test in the treated versus control group [150]. Another small placebo-controlled, double-blind, parallel-group pilot study randomized subjects with mild AD or amnestic mild cognitive impairment to rosiglitazone, a drug which improves insulin sensitivity and the regulation of APP processing, or placebo. Rosiglitazone was associated with better cognitive performance and with less decline in Aβ42 during the progression of AD [151]. Additional studies are needed to determine if glycemic control is a viable strategy to reduce the prevalence of cognitive impairment and dementia in the future.

Obesity—The United States, like other developed nations, has seen a dramatic increase in the number of overweight and obese adults, with estimates from 2003–2004 at 73.1% and 36.8%, respectively, for adults aged 40–59 years [152]. Since overweight and obesity are closely linked to hypertension, high cholesterol, and diabetes mellitus, a number of studies have assessed their association with dementia and AD. The findings from these studies have

been inconsistent, mostly related to a difference in when adiposity was measured during the life course. Studies that have examined overweight or obesity in midlife and the risk of dementia or AD have generally reported an increased risk [88,109,153,154,155,156,157]. In contrast, studies of late-life adiposity have shown a reduced risk of AD [158,159]. The findings in late life may be confounded by the fact that weight loss precedes the diagnosis of dementia [160,161,162]. Hence, this may be yet another situation with a nonlinear association, where higher adiposity in midlife increases the risk of dementia and its subtypes, with pathophysiologic changes associated with dementia then leading to declines in body mass in late life [123].

The most obvious mechanism by which midlife overweight or obesity may increase the risk of dementia in late life is through the increased risk of hypertension, diabetes, and hypercholesterolemia [153], which affect brain health in the same way as they do heart health. However, adjustment for these and other vascular conditions has not been shown to attenuate the association [157]; suggesting that overweight and obesity may also independently contribute to the risk of dementia. Alternative mechanisms include the effects of adipose tissue, which is metabolically active endocrine tissue that secretes several proinflammatory cytokines, hormones, and growth factors that cross the blood-brain barrier and affect brain health [153, 156]. For example, dysregulation of the hormone leptin with aging may directly contribute to AD neurodegeneration by increasing the deposition of Aβ in the brain [163].

General Anesthesia

Long-term cognitive problems have been reported in older adults following anesthesia and surgery [164], cardiac surgery in particular; suggesting that exposure to anesthesia or time spent “on pump” may increase the risk of cognitive impairment and dementia. Findings from case-control studies do not support an association [165,166]; however, one prospective study of early and midlife exposure to anesthesia and incident AD found that cumulative exposure to anesthesia increased risk, but only for exposures before, and not after, age 50 years [167]. A systematic review of the literature on the impact of anesthesia on the cognitive functioning of the elderly concluded that factors other than anesthesia (e.g. type of surgery) and other etiologic factors likely confound the association between anesthesia and risk of long-term cognitive deficits and dementia [168]. If exposure to general anesthesia in early or midlife increases the risk for cognitive impairment and dementia, it may be through structural brain changes or neuron loss that occurs during the anesthetized state [164], although this needs further investigation. Some investigators have suggested that some inhaled anesthetic agents at high concentrations interact with amyloid peptide [169] and induce Aβ oligomerization.

Head Injury

Head injury directly affects the structural and functional integrity of the brain and can lead to disturbances in consciousness and behavioral and cognitive deficits [170]. The association of head injury with an increased risk of cognitive impairment and dementia in late life has been examined in several epidemiologic studies. Based on cohort study findings, there appears to be strong evidence that head injury increases the risk of cognitive decline [171,172] as well as dementia and AD [173,174,175,176,177,178] with increasing severity [173,175]. The extent to which head injury influences the risk of cognitive impairment and dementia may depend on whether the head injury was accompanied by loss of consciousness and the duration of time between head injury and clinical onset. Guo and colleagues [173] reported the risk of AD was nearly ten times higher in persons who had a head injury with loss of consciousness compared to three times higher in those without loss of consciousness, and Schofield and colleagues [176] reported earlier onset of AD when loss of consciousness lasted longer than five minutes. A case-control study also suggested that the risk of dementia only is elevated within the first 10 years after head injury [179]. Genetic factors also may modify the association, where the

risk of dementia and AD and its pathology has been shown to be stronger in those with [175, 178,180,181] and without the APOE ε4 allele [172,181], but this has not been replicated in all studies [1701, 174,183].

Mechanisms that have been proposed to explain the association include damage to the blood brain barrier, increased oxidative stress, neuronal loss [184], and increased Aβ and tau pathology [185]. Additional studies of this association are needed that consider the nature and severity of the head injury in relation to the risk of cognitive impairment and dementia in late life. Prevention of head trauma is a laudable end in itself, whether or not it is eventually shown to ward off dementia. Children and adults should follow safety recommendations and laws to prevent head injury, such as wearing helmets while riding bicycles or motorcycles. Fall-related brain injuries in older adults should also be minimized through preventative measures.

Depression

Depression and cognitive impairment/dementia commonly co-exist making it challenging to determine whether depression is within the causal pathway leading to dementia (i.e. a true etiologic risk factor) or is a consequence of the disease (i.e. a prodromal clinical manifestation) [186]. Both hypotheses are supported in the literature, suggesting that there may not be one definitive answer [186]. Studies have shown elevated risk of subsequent dementia [187] and AD [188], while other prospective studies have not replicated such findings for cognitive decline [189] or dementia [190]. Inconsistencies between studies may be related to differences in the interval between depression and cognitive impairment or dementia onset, the use of depressive symptoms or clinical diagnosis of depression, or the cognitive outcome assessed (e.g. cognitive decline, mild cognitive impairment (MCI), and dementia). Findings that there is a stronger association when the interval is short supports the hypotheses that depression is a prodrome of dementia, while a longer interval suggests that depression is a true risk factor. Deficits in cognitive performance following a depressive episode do not completely subside after the depression remits [191,192], but it remains unknown whether these persistent deficits are symptoms of a progressive dementia syndrome. The cognitive outcome assessed could also have important diagnostic implications since the current clinical criteria for MCI does not consider depressive symptoms [12], whereas the diagnosis of dementia requires that it not be explained by another mental disorder, including depression [17].

Since findings from observational studies are inconclusive with respect to the temporal direction of the association between depression and dementia where the link between depression and cognitive dysfunction potentially may be explained by depression being a casual factor or a shared risk or confounding factor, or where the association is due to reverse causality or through an interaction with a third variable such as APOE ε4 [193], evidence from biologic studies of the link between depression and cognitive impairment and dementia is especially important. The proposed mechanisms have been outlined and depicted by Butters and colleagues [186]. Briefly, depression may be a true etiologic risk factor through chronically elevated glucocorticoid production, which may cause hippocampal atrophy and subsequent cognitive dysfunction. Conversely, depression may arise secondary to cognitive impairment and dementia due to frontostriatial damage and hippocampal volume loss caused by cerebrovascular or degenerative neuropathology [186].

Antidepressant treatment of depression with co-existing cognitive impairment does not seem to resolve all cognitive deficits even when the depression is in remission [191,192], or prevent cognitive problems from developing in those with normal cognition who are being treated for depression [191]. Continuous antidepressant drug use, however, has been associated with a reduced rate of cognitive decline in depressed patients already diagnosed with AD in comparison to non-depressed and depressed AD patients not continuously treated with antidepressants [194]. In a neuroimaging study, the degree of hippocampal atrophy was

associated with the duration of untreated depression [195]. At the present time, there are no published reports of randomized controlled trials of the impact of early and midlife antidepressant treatment on the occurrence of cognitive impairment and dementia in late life.

Personality

Research on personality and aging suggests that personality traits are relatively stable over time [196], but that life events, social change, or psychological processes of adjustment may contribute to personality change in mid and late life [197]. Only a few studies have examined the association between personality and the risk of cognitive impairment and dementia. Of the most widely recognized personality traits [i.e. neuroticism, extraversion, openness, agreeableness, conscientiousness; 198], higher neuroticism and psychological distress (another measure of neuroticism) have most consistently been shown to be associated with increased risk of cognitive impairment [199,200], AD [201] and with younger age at dementia onset in females [202]. Conversely, moderate extraversion in midlife may be associated with a lower risk of cognitive impairment [199] and high conscientiousness in late life may reduce the rate of cognitive decline and incident MCI and AD [203]. As with the biologic risk factors discussed earlier, behaviors and attitudes observed in later life may represent consequences of, or adaptations to, early signs of dementia. While it seems improbable that personality traits can be modified in order to improve cognitive health outcomes with aging, individuals facing aging-related cognitive challenges could potentially benefit from learning new compensatory strategies best suited to their own personality traits.

Leisure Activity

The level of engagement with the environment, including physical, cognitive, and social activity, has been suggested to influence cognitive health in old age. A number of studies have examined engagement in stimulating activities as a group and also as individual components in both humans and animals. Although physical, social and mental activities usually overlap, and studies have shown beneficial interactive effects for rate of cognitive decline [204,205], cognitive impairment [206], dementia [207,208], and AD [209,210]; the following section will present evidence for each type of activity separately. Note that the very attractiveness of the notion that voluntary leisure activity may stave off the onset of dementia can lead to confusing cause with consequence since both aging [211] and cognitive decline [204] are associated with lower engagement in activities.

Physical Activity—The importance of physical activity in physical health is well known, but the role of physical activity in brain and cognitive health has only recently received attention. Regular physical activity in early life (15 – 25 years) has been associated with faster processing speed ability in men in late life [212]. Two of three studies that assessed physical activity in midlife in relation to later risk cognitive impairment and dementia suggest that higher engagement in physical activity is associated with a reduced risk of dementia and AD [213, 214]. The third midlife study did not report a reduced risk of dementia in relation to increased physical activity [85]; however, the discrepancy may be due to the this study's measure of physical activity being based on both leisure-time and occupational physical activity, whereas the other two examined only leisure-time physical activity. A null association between midlife work-related physical activity only and risk of dementia and AD also was reported by Rovio and colleagues [215]. The absence of a protective effect for work-related physical activity may be due to confounding by the low intellectual demand of some occupations that require more physical labor (see occupation section), i.e. the two effects might have countered each other. The findings of other prospective studies with shorter follow-up intervals are also inconsistent with some reporting that regular exercise is associated with a reduced risk of cognitive impairment [216,217] dementia and AD [207,218,219,220] and vascular dementia [220,221], while others have not [206,222,223,224,225,226]. Only one randomized trial has been

conducted to confirm the observational findings of the effect physical activity has on cognitive function in older adults. A modest reduction in cognitive decline was observed in those who were assigned to the 6-month physical activity intervention compared to usual care over the 18-month follow-up period [227].

Physical activity may benefit cognitive health through several mechanisms. First, similar benefits seen in the cardiovascular system extend to the cerebrovascular system. This effect may be direct (e.g. through improved perfusion) or indirect through a reduction in other vascular morbidities including hypertension, diabetes, hypercholesterolemia, and obesity. Physical activity may also act through other pathways since most epidemiologic studies controlled for vascular factors and still found an effect [228]. A review by Rolland and colleagues [228] describes other potential mechanisms including increased neurogenesis, enhancement of brain cytoarchitecture (blood vessels, dendrites, microglia) and electrophysiological properties, increased brain growth factors, and neuropathological processes such as the formation of amyloid plaques in AD.

At this time, recommendations for physical activity as a means to improve cognitive health with aging are limited. Further research should unpack the type, intensity, frequency, and duration that most effectively reduce the risk of cognitive impairment and dementia. At best, aerobic exercise even at a low intensity may have a clinical impact on dementia prevention (e.g. playing golf or walking) [228]. Duration has not been assessed, but since AD-related neuropathology is believed to develop early in life, it is logical to assume that earlier introduction of exercise practices would exert a longer-term protective effect as it does for cardiovascular disease. However, as reviewed above, even studies of late-life physical activity suggest that there may be some benefit to cognition. In sum, appropriate physical activity should be encouraged at all ages for overall health promotion, although specific recommendations with regard to cognitive health await more research.

Cognitive Activity—There is interest in whether mentally stimulating activity benefits brain and cognitive health, analogous to the well established benefits of physical activity on physical health. Only two studies to date have prospectively examined the role of midlife cognitive activities on the risk of dementia in AD, and both included a twin analysis to control for genetics and unmeasured early-life environment. The results of each of these studies suggest that higher engagement in cognitively stimulating activities is associated with a reduced risk for dementia [209,223] and AD for women [209]. Prospective studies of late-life cognitive activity and risk of cognitive impairment and dementia have generally found that more frequent participation in cognitive activity is associated with a reduced rate of cognitive decline [229] and a reduced risk of cognitive impairment [206,225], dementia [207,208,224], and of AD [226,230]. Conversely, engagement in leisure activities that are characterized as low cognitive demand, such as watching television, have been found to be associated with an increased risk of cognitive impairment [206]. However, once again, caution must be exercised in distinguishing cause from consequence.

There are currently no randomized trials that have examined the effect of cognitive activity on the risk of cognitive impairment or dementia. The potential effectiveness of cognitive activity can be surmised from intervention programs that have trained healthy older adults on specific cognitive abilities and tested whether performance in these domains improved. A review by Acevedo and Loewenstein [231] summarizes the findings of these trials. One randomized trial that stands out is the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study [232]. In this large study, community-dwelling older adults were trained in one of four cognitive areas (i.e. memory, reasoning, speed of processing, and control) during 10 group sessions over a period of five to six weeks with four booster sessions at 11 and 35 weeks post-intervention. Assessment of cognitive and functional measures at the two and five

year follow-ups revealed improvement on the domains trained, but little transfer to other domains or to functional abilities (e.g. IADLs). Conversely, other randomized trials conducted since the ACTIVE study have found transfer to everyday activities [233,234,235] and psychosocial measures [236] following training. Based on these trials, as well as evidence of improvement in cognitive function in patients with both non-progressive (e.g. stroke) and progressive neurological conditions (e.g. AD) following cognitive interventions [231], there appears to be the potential to reduce the risk of cognitive impairment and dementia through cognitive interventions. Future well-designed randomized controlled trials of cognitive and multimodal training programs should be conducted in diverse populations and assess the impact on both cognitive and everyday activities.

Engaging in mentally stimulating activities may be considered the most direct strategy to increase brain reserve. Studies in rodents have shown that mental exercise induces neurogenesis [237,238] and synaptogenesis [239], increases hippocampal synaptic reactivity [240], enhances cerebrovasculature [241], and reduces brain beta-amyloid deposition [240, 242]. Human studies have demonstrated that cognitive activity may lead to a reorganization of neurocognitive networks [243], attenuates the adverse effects of stress hormones on the brain [244], and modifies the association between white matter lesion density, reflective of small vessel disease, and cognitive performance [245]. Taken together, these findings suggest that engagement in cognitive activities may increase compensation for brain pathology by increasing brain reserve, which may delay or even prevent the clinical onset of cognitive impairment and dementia within the individual's lifetime.

Social Activity—Studies to date have found associations of cognitive health with different aspects of social activity. For example, a larger social network [246,247,248,249,250], more emotional support [251], and higher level of social engagement and social integration [208, 249,250,252,253,254] in late life have been shown to be associated with a reduced rate of cognitive decline and lower risk for dementia. Moreover, social network size has also been shown to modify the association between AD pathology and level of cognitive function [255] and level of social activity has been shown to precede, rather than follow, cognitive change over time [256]. Variations in findings may be due to differences in how social activity is measured or what cognitive outcome was measured, but also in characteristics of the specific populations that were studied.

There are several reasons why social activity of different types may be related to cognitive functioning in older age. Most often proposed is that social relations impact health factors that are also related to cognitive functioning, such as vascular conditions [257,258] and depression [259,260], or improve health behaviors, such as maintaining a physical exercise routine or adhering to medical treatments [261]. Social activities may also benefit cognitive function through a cognitively stimulating environment [246,251,255]. Regardless of how social activity affects cognitive functioning in late life, it seems that avoiding social isolation and maintaining various types of social activities may be protective against cognitive impairment and dementia in late life. The possibility of reverse causality should also be borne in mind, given that neuropathology appears to begin decades before symptoms are noted.

Alcohol Use

Most previous studies of alcohol and cognition have focused on the negative effects of excessive alcohol consumption. However, evidence suggests that light-to-moderate alcohol consumption, in comparison to abstinence or heavy drinking, may have cognitive health benefits including lesser decline on multiple cognitive domains [262]. A meta-analysis of the prospective association between alcohol use and cognitive decline and dementia (including AD and VaD) concluded that low to moderate intake is associated with a reduced risk of

dementia and AD, whereas the risk of VaD and cognitive decline is reduced but not statistically significant [263]. Two studies of midlife alcohol drinking and the risk of cognitive impairment and dementia in late life also both found support for a protective effect of moderate alcohol drinking. Specifically, Anttila and colleagues [264] found a U-shaped relation and effect modification by ApoE e4 allele in a Finish population with 23 years of follow-up, and Mehlig and colleagues [265] reported that a higher frequency of wine, but not spirits or beer, consumption in midlife was associated with a lower incidence of dementia 34 years later in Swedish women when time-varying covariates were adjusted for. It is noteworthy that this study and others [266] have found that the benefits of moderate alcohol consumption are greater in or restricted to women, although not all studies have replicated this effect [267].

In contrast to the deleterious effects on the brain following acute intake or chronic abuse of alcohol, consuming alcohol in moderation may benefit brain health. One potential mechanism is though the reduction of various cardiovascular risk factors [268] such as increasing HDL cholesterol levels, enhancing insulin sensitivity, and reducing inflammatory reactions, blood pressure, blood clotting, plasma homocysteine, white matter hyperintensities, and sub-clinical infarcts. Other potential mechanisms include increased social engagement [269], which may increase brain reserve, antioxidant and anti-amyloidogenic effects of flavonoids found in red wine [270,271], and upregulation of hippocampal acetylcholine [272].

Randomized controlled trials of alcohol use are neither feasible nor ethical. Recommendations for the use of alcohol as a strategy to reduce the risk of cognitive impairment or dementia in old age will have to be based upon well-designed prospective observational studies that determine the optimal type, level, and duration of intake balanced against the potential negative impacts of alcohol on the aging brain.

Tobacco Use

Early studies of the relation between smoking and dementia suggested a protective effect of smoking; however, longitudinal studies have largely attributed these findings to survivor bias [273]. This is a prime example of how the association between an exposure and increased mortality can lead to biased samples (i.e. fewer smokers reach the age of greatest risk for dementia) and can distort the association with cognitive health. Consequently, the most convincing evidence comes from studies that have taken the life course approach and examined the association between midlife smoking patterns and the risk of cognitive impairment and dementia in late life. Using data from the HAAS of Japanese-American men, the risk of cognitive impairment was found to be greater for continuous smokers and those who had quit during the follow-up period compared to never-smokers [274], and the risk of AD was found to be greater in medium and heavy compared to light smokers [275]. The results of a meta-analysis of the association between smoking and dementia and cognitive decline in other prospective studies demonstrates that current smoking increases the risk of dementia and cognitive decline in comparison to never smoking. Whether or not “ever smoking” or being a “former smoker” increases or decreases the risk is unclear due to measurement variations between studies [276]. To our knowledge, no randomized controlled trials have yet been reported of the impact of smoking cessation on late-life cognitive health, which may help tease apart the intensity and duration of smoking, and its interactions with other risk factors, that are associated with cognitive health in old age.

Tobacco smoke has been stated as “the single most significant source of toxic chemical exposure to humans” [277]. It is associated with increased morbidity and mortality related, but not limited, to cardiovascular disease, cerebrovasclar disease, chronic obstructive airways disease, and lung cancer [277]. Short-term nicotine intake, which is the primary and addictive component of tobacco smoke, can have positive effects on cognition, specifically attention, learning, and memory, by facilitating the release of the neurotransmitters acetylecholine,

glutamate, dopamine, norepinephrine, serotonin, and γ-aminobutryic acid [278]. However, long-term exposure to tobacco smoke has been shown to have several adverse outcomes on the brain that contribute to an increased risk of cognitive impairment and dementia in late life. These include increased silent brain infarcts, white matter intensities, neuronal death, and subcortical atrophy. Smoking also lowers the level of circulating antioxidants that scavenge free radicals, heightens the inflammatory response, and leads to atherosclerosis that affects permeability of the blood-brain barrier, cerebral blood flow, and brain metabolism [277]. Finally, smoking may directly influence dementia pathology by increasing the number of plaques [275].

Postmenopausal Reproductive Hormone Therapy

Early observational studies of postmenopausal hormone therapy (previously referred to as hormone replacement therapy or HRT) suggested that it may reduce risk of cognitive decline [279]; however, results from a randomized placebo-controlled trial as part of the Women's Health Initiative (WHIMS) reported no benefit to global cognitive function [280,281] or risk for MCI [282], and an increased risk of probable incident dementia [282] in postmenopausal women aged 65 years or older. One study found, however, that elevated risk of incident AD in older women was reduced to the same level in men if they had received postmenopausal reproductive hormone therapy for at least 10 years [283], suggesting that this therapy may still benefit cognitive health if started in perimenopausal women and in women soon after menopause. More conclusive evidence is needed before postmenopausal reproductive hormone therapy can be recommended as a strategy to reduce the risk of cognitive impairment or dementia.

Non-Steroidal Anti-Inflammatory Drugs

Inflammation is known to play a role in dementia, possibly as both an initiator and accelerator of pathological brain changes [284]. Therefore, the potential for anti-inflammatory agents to reduce the risk of cognitive impairment and dementia is of interest. Observational studies have demonstrated support for a protective effect of non-steroidal antiinflammatory drugs [285, 286,287], but RCTs have not found similar protective effects [287,288,289]. Possible reasons for the discrepancy include the timing of NSAID treatment or the type and dosage of NSAID investigated [290]. In fact, an observational study reported a slower rate of cognitive decline when NSAID use began in midlife compared to late life, especially for those with one or more APOE ε4 alleles [291,292]. At this time, no recommendation can be made as to whether or not NSAIDs may be effective in AD prevention. To determine the effect based on whether they are prescribed as early as possible in the disease process, even during the presymptomatic stage, requires very long-term controlled trials that also test the safety of long-term NSAID use.

Ginkgo Biloba

Ginkgo biloba is an herbal supplement that has been widely marketed as a memory and concentration enhancer. Its antioxidant properties [293,294], its ability to promote blood flow to the brain [295], and/or its affect on Aβeta metabolism [296,297] suggest that it may potentially benefit cognitive function. Observational and RCTs that have examined its ability to slow cognitive decline or reduce the risk of cognitive impairment or dementia have revealed both positive [298,299] and negative [300] findings. Until recently, no study had examined Ginkgo biloba as a primary prevention method. Dodge and colleagues [301] conducted a randomized, placebo-controlled trial to examine the effect of Ginkgo biloba on cognitive decline (defined as transition from clinical dementia rating [302] score 0 to 0.5) over 42 months in 118 older adults. They found that the Ginkgo biloba group did not have a reduced risk of cognitive decline compared to the placebo group, but that a protective effect was observed when medication compliance was controlled for. The Ginkgo Evaluation of Memory (GEM)

study, a large, randomized, double-blind, placebo-controlled clinical trial of the effect of Ginkgo biloba versus placebo on incident dementia and AD over 6 years, reported that Ginkgo biloba did not reduce the incidence of dementia or AD in cognitively normal or MCI participants [303]. The results of another ongoing, larger, long-term trial of Ginkgo biloba, known as the GuidAge study [304], may provide more conclusive evidence of whether Ginkgo biloba is effective in the prevention of dementia.

Diet/Nutrition

Diet is an important part of a healthy lifestyle and influences the risk of several diseases and the aging process in general. Studies of the associations between micro- and macro-nutrients and cognitive functioning in old age have examined both dietary and supplemental intake with dietary sources generally exhibiting stronger effects.

Micronutrients—Vitamins B6, B12 and folic acid may reduce the risk of cognitive impairment and dementia since blood levels of homocysteine have been shown to be elevated in cognitive impairment and AD and contribute to pathology through vascular and direct neurotoxic mechanisms [305]. Thus, the beneficial effects of vitamin B12 supplementation should only be observed in individual who are B12 deficit, which occurs more in older adults due to increased difficulties in absorption due to gastritis or other digestive conditions [306]. However, 10 months of vitamin B12 supplementation was not found to improve cognition in demented patients with vitamin B12 deficiency [307], and a Cochrane Database Review of vitamin B12 supplementation and cognitive function in late life concluded that B12 supplementation, compared to placebo, does not improve cognitive function in dementia patients who have low serum levels of vitamin B12 [308]. Similarly, randomized controlled trials of folate, vitamin B6, and vitamin B12 supplementation have not shown a beneficial effect on cognitive function in normal [309] or already impaired patients [305,309].

Given that free radicals and oxidative damage have been implicated in age-related brain disease [310,311], intake of antioxidants (e.g. Vitamins C and E) has also been suggested as a way to reduce the risk of cognitive impairment and dementia. However, there are conflicting reports in the literature. For example, dietary and supplemental intake of vitamins C and E has been associated with a lower risk of incident Alzheimer's disease [312,313], and higher midlife consumption of fruits and vegetables, good sources of antioxidants, has been found to reduce the risk of dementia and AD [314]. In contrast, other studies reported no association between antioxidant substances collected in midlife [315] or late-life [316] and dementia.

Higher intake of polyphenols from fruit and vegetable juice [317] and flavonoids from fruits and vegetables, red wine, and tea [318], which are types of antioxidants, have been found to be associated with a reduced risk of dementia and Alzheimer's disease. Dark chocolate and cocoa also contain high concentrations of flavonoids. Dark chocolate and cocoa have been shown promote cardiovascular health through mechanisms related to blood pressure reduction [319,320], increased insulin sensitivity [320], LDL cholesterol reduction [319,321], reduced platelet reactivity [321], improved endothelial function [322], and reduced inflammation [321,323], with potential impact on brain and cognitive health. Thus, an association between dark chocolate and cocoa consumption and risk of cognitive impairment and dementia seems plausible and is beginning to be examined. One double-blind, placebo-controlled, randomized trial of the effects on neuropsychological functioning showed that 6 week consumption of dark chocolate and cocoa did not benefit performance on tests of memory, executive function, or attention [324]. Longer-term studies are warranted given dark chocolate and cocoa's cardioprotective effects and a report that cocoa has anti-neurodegenerative effects by protecting against Aβ-induced neurotoxicity *in vitro* [325].

If antioxidants and their sub-types do in fact offer protection against cognitive impairment and dementia, potential mechanisms include: 1) increasing brain reserve, 2) reducing cerebrovascular disease, and 3) decreasing oxidative stress and inflammation that contributes to changes in the brain with aging and pathological processes associated with dementia [311].

Macronutrients—A macronutrient that stands out for its role in cognitive functioning is dietary fat. Using data from the Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) study, Laitinen and colleagues [326] found an association between midlife fat intake from spreads and milk and risk for dementia and AD 21 years later. Specifically, moderate (compared to low) intake of total fats and unsaturated fats from spreads (e.g. butter or butter-oil mixture, margarine/light spread) was associated with reduced risk of dementia and AD, whereas a moderate intake of saturated fats from spreads was associated with increased risk. Most other longitudinal studies of the association between dietary fats have had relatively short follow-up periods ranging from about 4 to 8.5 years [312,327,328,329,330], but have reported similar findings for both cognitive decline and dementia. One randomized, controlled trial of the effect of fish oil, which is a source of polyunsaturated fatty acids including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on cognitive performance observed no overall effect of fish oil supplementation in older adults, but small effects for APOE ε4 carriers and males for the specific cognitive domain of attention [331]. The authors conclude that the intervention duration of 26 weeks may have been too short and that trials of longer-term interventions are warranted. The primary mechanism by which fats are thought to play a role in cognitive impairment and dementia is through blood cholesterol levels; although studies in rodents suggest that dietary fat also may be involved in amyloid deposition [332,333].

Greater consumption of caffeine also has been found to reduce cognitive decline in women, [334], to reduce the incidence of dementia [335], and to be associated with reduced risk of AD in a retrospective study that measured caffeine consumption over a 20 year period prior to AD assessment [336]. The beneficial effects of caffeine may be through mechanisms that reduce Aβ production [337] or by increasing the level of brain proteins important for learning and memory such as brain derived neurotrophic factor [338].

Dietary Patterns—Much research to date has focused on specific nutrients, however, what may produce the most benefits to cognition are whole foods, interactions of nutrients, or patterns of diet, and not just the nutrients or supplements themselves [339]. Although analyses using dietary patterns may be difficult to replicate across studies and may be subject to certain statistical biases [340,341], this method may also yield a representation of diet that is relatively stable over time [342] and may offer a better test of diet-related risk of disease than testing single diet items [343]. One dietary pattern that has been studied with respect to cognitive health so far has been the Mediterranean diet, which is typically represented by high intake of fruits, vegetables, whole-grain products, and fish. Higher adherence to the Mediterranean diet was associated with a reduced risk for AD [344]. Closer examination of dietary patterns should be included in future studies of the relationship between diet and cognitive functioning with aging.

In sum, evidence supports an association between diet/nutrition and cognitive health with aging. Before we can make specific recommendations, though, we should take heed of the following statement from the IANA task force on nutrition and cognitive decline with aging. “It is important to stress the need to develop further prospective studies of sufficiently long duration, including subjects whose diet is monitored at a sufficiently early stage or at least before disease or cognitive decline exist. Meta analyses should be developed, and on the basis of their results the most appropriate interventional studies can be planned. These studies must control for the greatest number of known confounding factors and take into account the impact

of the standard social determinants of food habits, such as the regional cultures, social status, and educational level." [345]

FUTURE DIRECTIONS: CHALLENGES AND RECOMMENDATIONS

As demonstrated by this review, few studies have examined risk factors more than a few years prior to dementia onset, which does not permit discrimination between a true independent risk factor and a prodromal or early symptom. In order to accomplish this, a life course approach needs to be taken. Life course epidemiology presents challenges in terms of both design and analysis. First, it entails more than collecting exposure data across the life span; temporal associations and inter-relationships must also be examined. Second, obtaining data at birth and again at multiple time points during the life span on both psychosocial and biologic exposures is rare, but even when such data exists with limitations (e.g. missing biologic data or data from a subset of participants) it can be valuable. Finally, the complexity of life course data requires sophisticated analytical techniques that are currently under-utilized such as structural equation modeling, path analysis, G-estimation, and multi-level modeling, and will likely stimulate new statistical methods [346]. Despite these challenges, the life course approach can be applied when data from cohorts from the same population but different time periods is available, or from historical cohorts, record linkage studies, or naturalistic studies. Finally, case-control studies of retrospectively collected exposure data or proxies for earlier life measures also may be used, although the validity of such exposures may be biased [346].

Randomized controlled trials are one of the best tools to test causal mechanisms and examine whether a factor is a true etiologic risk factor or a consequence of incipient dementia, and to evaluate the efficacy and effectiveness of a potential intervention. Generally, public health recommendations should not be made until large-scale RCTs, or viable alternatives, consistently replicate the findings from observational studies demonstrating a protective effect of an exposure. It must also be acknowledged, however, that some potentially causal exposures may not be amenable to intervention studies due to unethical or impractical reasons. For example, a randomized trial of cigarette smoking is unlikely to be proposed or supported for obvious ethical reasons. A randomized trial of a less harmful substance or exposure with a small effect may require a large number of participants to be followed for decades to detect a significant protective effect. The cost of a multi-decade trial would be prohibitive, and adequate levels of adherence and retention may be impossible to achieve. The clinical endpoint of RCTs is another intrinsic limitation since there is no "gold standard" to assess the validity of the clinical state (normal, cognitive impairment, dementia). The timing of the intervention may also introduce an additional challenge if, for example, the preventative effect is only observed if the treatment is initiated in early or midlife or during a critical period as was suggested for postmenopausal hormone therapy.

Logistic difficulties that render an intervention trial impractical should not lead to dismissal of potential scientific truth, but rather to develop more ingenious alternative study designs. West and colleagues [347] provide recommendations for addressing research questions when the RCT is not feasible. They propose the randomized encouragement design, the regression discontinuity design, interrupted time series analysis, and rigorous observational studies as potential alternative designs to the RCT. They emphasize that when employed correctly (i.e. assumptions and threats to validity are considered), these alternatives can be nearly as powerful as RCTs, especially when supplemented with advanced statistical approaches and replicated in numerous studies. It is now the task of researchers examining the role of these risk factors in cognitive impairment and dementia to adopt these alternatives to strengthen causal inferences that can be drawn.

Aside from the challenges of empirically testing a potential intervention either using a RCT or an alternative, it is also important to consider the risk-benefit ratio of candidate interventions. It particular, the safety, cost, and ease of modifiability should be taken into account. For example, factors such as diet and exercise may pose minimal safety risks even if implemented over a long period of time, are relatively affordable for everyone, and can easily be modified (with the exception of health promotion barriers discussed later), while testing the potential benefits of long-term hormone therapy in women already has been shown to be associated with increased health risks, is costly, and is not easily accessible. On the other hand, the benefits of behavioral changes, such as diet and exercise, may be small from a population-based perspective due to their broad influences on health and may be difficult to maintain, while medication adherence requires less effort and may more effectively target a biological mechanism associated with dementia and have a larger beneficial effect. Public health interventions aimed to reduce hypertension, diabetes, obesity, and cancer may shed light on whether these interventions also contribute to a reduction in the burden of cognitive impairment and dementia either indirectly, or through ancillary studies.

Another major hurdle is developing and implementing health promotion interventions to maintain cognitive health in old age. Since the etiology of cognitive impairment and dementia is multifactorial, the most effective prevention approach may require that multiple behaviors are modified simultaneously. However, such multidomain interventions will be challenging with respect to having a representative sample (i.e. participants who volunteer or adhere to the treatment intervention in an RCT are a select group), evaluation of the actual behavior, adherence in general, and how to assess the independent effects of each factor when they may be acting through common biologic pathways [33]. The transtheoretical model of health behavior change posits six stages of change that individuals progress through: precontemplation, contemplation, preparation, action, maintenance, and termination [348]. According to this model, successful behavioral change occurs when stage-matched interventions are implemented. Thus, it is important that researchers consider these stages at the individual level as well as other psychosocial factors that influence health promotion (e.g. ethnic/cultural values, social support, etc.) when designing and evaluating interventions studies for cognitive impairment and dementia prevention.

CONCLUSION

The loss of cognitive abilities is one of the most feared outcomes of aging. Unfortunately, up to half of the 85 years and older population suffers from some form of cognitive impairment [3], making the fear a reality for all too many. With the aging of our society, maintaining cognitive health in late life is a public health priority. This review provides a summary of the evidence regarding modifiable risk factors that are being examined for their potential role as a strategy to prevent or delay cognitive impairment and dementia in late life. The majority of findings thus far are based on cross-sectional or prospective observational studies with short follow-up periods. It is unclear whether the associations found represent a cause or consequence of incipient dementia, with various other methodological issues also potentially affecting the interpretation of the findings. Furthermore, it is worth restating that these factors are hypothesized to prevent or delay cognitive impairment and dementia by contributing to brain/cognitive reserve, rather than slowing neurodegeneration per se. Therefore, caution must be exercised when making recommendations to middle aged adults until additional well-designed observational studies embracing the life course approach, and/or RCTs when feasible, are conducted. In the interim, clinicians should assess the potential benefits and detriments of each strategy for their individual patients, in terms of both cognitive health and other health outcomes, keeping in mind that there is little evidence at this time to suggest that the risk of cognitive impairment or dementia will actually be reduced.

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