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Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective

Matthew Baumgart[a], Heather M. Snyder[b,*], Maria C. Carrillo[b], Sam Fazio[c], Hye Kim[a], Harry Johns[d]

[a]*Division of Public Policy, Alzheimer's Association, Washington, DC, USA*
[b]*Division of Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA*
[c]*Division of Constituent Relations, Alzheimer's Association, Chicago, IL, USA*
[d]*President & CEO, Alzheimer's Association, Chicago, IL, USA*

Abstract An estimated 47 million people worldwide are living with dementia in 2015, and this number is projected to triple by 2050. In the absence of a disease-modifying treatment or cure, reducing the risk of developing dementia takes on added importance. In 2014, the World Dementia Council (WDC) requested the Alzheimer's Association evaluate and report on the state of the evidence on modifiable risk factors for cognitive decline and dementia. This report is a summary of the Association's evaluation, which was presented at the October 2014 WDC meeting. The Association believes there is sufficient evidence to support the link between several modifiable risk factors and a reduced risk for cognitive decline, and sufficient evidence to suggest that some modifiable risk factors may be associated with reduced risk of dementia. Specifically, the Association believes there is sufficiently strong evidence, from a population-based perspective, to conclude that regular physical activity and management of cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) reduce the risk of cognitive decline and may reduce the risk of dementia. The Association also believes there is sufficiently strong evidence to conclude that a healthy diet and lifelong learning/cognitive training may also reduce the risk of cognitive decline.

Keywords: World Dementia Council; Alzheimer's Association; Alzheimer's disease; Cognitive decline; Dementia; Risk factors; Modifiable risk factors; Cardiovascular disease risk factors; Lifestyle risk factors; Physical activity; Diabetes; Obesity; Smoking; Hypertension; Diet; Lifelong learning; Cognitive training

1. Introduction

An estimated 47 million people worldwide are living with dementia in 2015 [1], and this number is projected to triple by 2050 [2]. In the absence of a disease-modifying treatment or cure, reducing the risk of developing dementia takes on added importance. Even when effective treatments become available, risk reduction will likely remain a fundamental strategy in reducing the number of individuals affected; for many non-communicable diseases with available treatments (such as diabetes, cancer, and heart disease), risk reduction efforts remain a major component of the campaigns against these diseases.

As a science-based advocacy organization, the Alzheimer's Association—the largest voluntary health organization dedicated to Alzheimer's disease and other dementias—is the global nonprofit leader in Alzheimer's disease research and the leading resource for more than 5 million individuals living with the disease in the United States and their caregivers. In this role, we are often asked for both expertise and guidance related to risk reduction for Alzheimer's disease. The Association monitors the science and develops its positions accordingly.

*Corresponding author. Tel.: 312-335-5184; Fax: 866-875-2553.
E-mail address: hsnyder@alz.org

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In December 2013, the G8 nations—Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, and the United States—created the World Dementia Council (WDC) [3] to provide global advocacy and leadership on key dementia challenges. The WDC is composed of individuals from around the world with a wide range of expertise and from a wide range of disciplines. One of the WDC's priority areas is potential risk reduction, both in the absence of treatments and after the time at which a treatment or treatments become available. However, the WDC also recognized that any public health effort to address the risk factors of cognitive decline and dementia must be grounded in the scientific evidence and informed by the scientific literature. The WDC requested the Alzheimer's Association evaluate and report on the state of the evidence on modifiable risk factors for cognitive decline and dementia to support the WDC in any future recommendations.

The Association's task was not to conduct an independent review of all published literature related to risk reduction, but to evaluate the existing reviews, briefly summarize the findings about the existing body of published evidence, and draw conclusions about the current state of the science. The Alzheimer's Association began by reviewing the detailed reviews prepared by the UK Health Forum for the Blackfriars Consensus [4], Alzheimer's Australia [5,6], Alzheimer's Disease International [7], and Deborah Barnes, PhD, and Kristine Yaffe, MD [8]. Of the articles cited in these reviews, the Association paid particular attention to meta-analyses, systematic reviews, and Cochrane reviews; in addition, the Association evaluated more recently published studies on specific modifiable risk factors. The Association consulted with more than a dozen leading researchers and experts in the dementia risk reduction field—both as part of a pre-existing effort on risk reduction and specifically for this effort—to obtain their input on the current state of the science and the completeness and accuracy of our summary and conclusions.

The Alzheimer's Association—from both a scientific and population-based perspective—weighed the evidence for cognitive decline and all-cause dementia based on the consistency of previous reviews, meta-analyses, and scientific peer-reviewed publications; the number and strength of individual studies (including the number of participants, duration of the study, and diversity of the participants); and the types of those studies (prospective, longitudinal, observational, or randomized controlled trials). The summary of the Association's evaluation was presented at the October 2014 WDC meeting and is presented in this report. Since the WDC meeting, the Association has reviewed additional, more recently published abstracts and studies, which were added to this report. These studies did not change the original underlying conclusions reported to the WDC.

2. Summary of the evidence of individual risk factors

The greatest risk factors for late-onset "sporadic" Alzheimer's disease and other dementias are age [9–11], family history [12–15], and genetic susceptibility genes, such as the Apolipoprotein E ε4 allele [16,17]. However, none of these risk factors can be modified by medical interventions or by individual behavior. A 2010 National Institutes of Health (NIH) *State of the Science* conference found insufficient evidence, on a clinical level, to support the association of any modifiable risk factors and Alzheimer's disease [18]. The evidence in many cases (particularly with respect to dementia as opposed to cognitive decline) is inconclusive due in large part to the limited data collected to date and the limited number of clinical studies involving specific interventions.

However, despite the limitations of the literature, looking at analyses and studies since the 2010 NIH *State of the Science* conference and viewing the data from a population-based health perspective rather than a clinical perspective, we believe there is sufficient evidence: (a) to support the association between several modifiable risk factors and a reduced risk for cognitive decline; and (b) to suggest that some modifiable risk factors may be associated with reduced risk of dementia. This report discusses these risk factors. Conclusions are summarized in Figures 1 and 2.

3. Cardiovascular risk factors

3.1. Diabetes

Based on several meta-analyses, systematic reviews, and recent studies, more than a dozen prospective, observational, and longitudinal studies have shown lower cognitive performance and an increase in the risk of dementia among individuals with diabetes; on balance, the association between diabetes and dementia appears strong, but not conclusive [19–26]. Further, a recent meta-analysis demonstrated that individuals with mild cognitive impairment (MCI) and diabetes were more likely to progress to dementia than individuals with MCI and no diabetes [27]. Some evidence suggests diabetes increases dementia risk not only through vascular pathways but also through interactions of other biological mechanisms related to diabetes itself [28–30].

3.2. Mid-life obesity

Based on several meta-analyses, systematic reviews, and individual studies, evidence from at least a half dozen prospective studies found that mid-life obesity is associated with an increased risk of dementia. Most postulate this is a strong link, especially with regard to cognitive decline [20,22,31–36]. The association may change with age, as being overweight—and, even possibly being obese—in later life has been associated with reduced risk of dementia [37–41]. And, a recent, large, retrospective cohort study found a lower risk for dementia among those who were overweight even in midlife, while those who were underweight had an elevated risk [42].

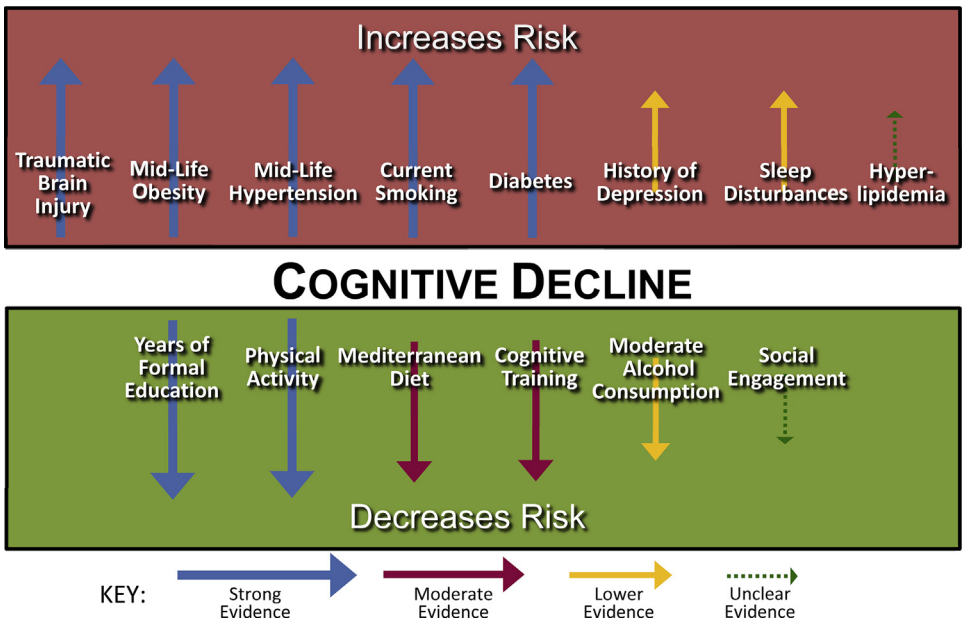

Fig. 1. Strength of evidence on risk factors for cognitive decline.

3.3. Mid-life hypertension

Meta-analyses of clinical trials and prospective, observational, longitudinal, and cross-sectional studies, including a Cochrane review, have not indicated a consistent relationship between high blood pressure and dementia; there is stronger evidence for a link with cognitive decline [43–47]. A systematic review of meta-analyses, observational studies, and randomized controlled trials found treatments of hypertension may reduce the risk of cognitive decline [48]; a meta-analysis of longitudinal studies concluded the opposite [49]. Similar to data on the link between obesity and cognitive decline/dementia, studies demonstrate that later-life hypertension may be protective against cognitive decline [50,51].

3.4. Hyperlipidemia (elevated cholesterol)

Systematic reviews of prospective studies have found mixed results for the relationship between both mid-life and late-life high cholesterol levels and dementia, including no association between cholesterol levels and vascular dementia [52,53]. While some observational studies have

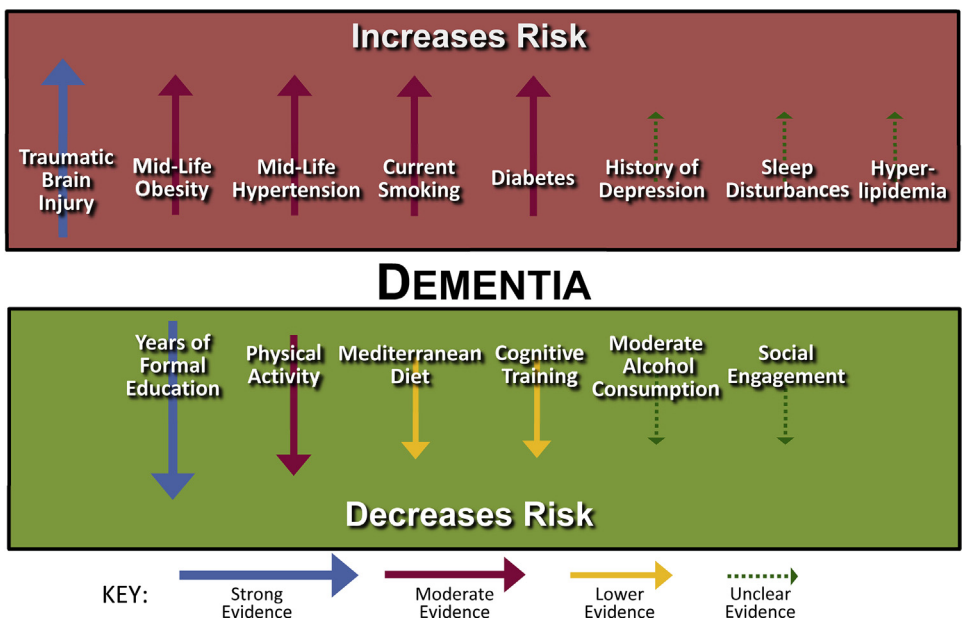

Fig. 2. Strength of evidence on risk factors for dementia.

suggested that statin medications used to control cholesterol levels may reduce the risk of dementia [44,54,55], a Cochrane review and systematic reviews found no or inconsistent evidence that use of statins reduces risk [56–58]. The effect has not been seen to date in trials and high-quality cohort studies.

4. Lifestyle risk factors

4.1. Current smoking

According to several systematic reviews and meta-analyses, prospective and longitudinal studies have found strong evidence that current smoking increases the risk of cognitive decline and possibly dementia [7,26,35,59–64]. Quitting smoking may reduce the associated risk to levels comparable to those who have not smoked [7,63–65]. One study of a large multi-ethnic cohort found heavy smoking in middle-age as much as doubled the risk of later-life dementia [66].

4.2. Physical activity

According to systematic reviews and meta-analyses, more than 20 prospective, longitudinal, and cross-sectional studies, as well as randomized controlled trials, have shown physical activity—even in some cases, mild physical activity such as walking—is associated with a decreased risk of cognitive impairment and/or improved cognitive function [35,62,67–76]. Several randomized controlled trials and a Cochrane review of such trials have found that inactive, but otherwise healthy, seniors who begin an exercise program experience significantly improved cognitive function [77,78]. Studies most consistently demonstrate the exercise must be regular and tend toward the more vigorous side [69–72,74]; however, to date, they have failed to pinpoint the optimal duration of the activity, the type and intensity of the exercise, and what period during a person's lifespan it should occur that would maximize potential protective effects.

4.3. Diet

Information on the effects of various aspects of diet (including various nutrients and vitamins, foods, or food groups) on reducing risk is limited and conflicting. Given that many elements of diet are interrelated and interactive, the idea of a whole dietary pattern approach has gained some ground. However, interpretation is challenging as dietary pattern often varies with other lifestyle factors and with demographic variables that may also have an impact on risk. A few cohort studies on the Mediterranean diet (relatively little red meat with an emphasis on whole grains, fruits and vegetables, fish, nuts, and olive oil) or a combined Mediterranean-DASH (Dietary Approaches to Stop Hypertension) diet suggest an association between these diets and reduced risk [79–81].

4.4. Alcohol

Meta-analyses of prospective and case control studies of older adults suggest small or moderate alcohol consumption by older individuals may decrease the risk of cognitive decline and dementia [82–84]. The evidence is not strong enough, however, to suggest those who do not drink should start drinking, especially when weighed against the potential negative effects of excessive alcohol consumption, such as an increased risk of falls among older adults [85–87].

4.5. Cognitive training

A Cochrane review found three dozen randomized controlled trials of mental engagement/cognitive training interventions showing improvements in immediate and delayed recall among those in the treatment group compared with the control group [88]. Systematic reviews of observational studies and randomized controlled trials reached similar conclusions [89,90]. However, based on these analyses, it is unclear whether the improvement is attributed specifically to the cognitive intervention. Despite the large number of trials, most were fairly small, and the data overall were inconclusive. And, as with physical activity, the "recipe" for any successful engagement remains unknown.

4.6. Social engagement

There are very few systematic reviews of the evidence on social engagement—such as doing volunteer work, joining a club, or going to church—as a potential protective factor against cognitive decline or dementia [91]. Some individual studies have shown that social activities, larger social networks, and a history of social contact are associated with better cognitive function and reduced risk for cognitive decline [92–101]. However, an independent coordinated analysis of four longitudinal studies found no effect on cognitive functioning [102]. Looking at the totality of the evidence, most studies in this area are small, are combined with cognitive training and/or physical activities (making it difficult to disaggregate the potential benefits solely of social engagement), and/or are too dissimilar in types of social engagement to draw any conclusions.

5. Other risk factors

5.1. Years of formal education

Among potentially modifiable risk factors, the most consistent evidence surrounds years of formal education (years of schooling in a classroom-based setting taught by professionally trained teachers). People with more years of formal education (measured by grade level attained and/or college attendance) or greater literacy have a lower risk for dementia than those with fewer years of formal education [62,103–111].

5.2. Traumatic brain injury

Solid evidence exists that moderate and severe traumatic brain injury (TBI) increases the risk of developing certain forms of dementia [112–117]. And those who experience repeated head injuries (such as boxers, football players, and combat veterans) may be at an even higher risk [118–124]. While it is not known what specific aspect of TBI (force, repetitiveness, etc.) leads to disrupted brain function, these multiple studies taken together strongly link TBI to increased risk of cognitive decline and dementia.

5.3. Depression

Meta-analyses of cohort and longitudinal studies, as well as additional cohort studies, have shown a history of depression increases the risk for dementia [125–127]. While a recent cohort study found depressive symptoms are independently associated with cognitive decline [128], questions remain regarding whether depression may increase an individual's risk or be an early marker of brain changes associated with dementia. In addition, the effect of treatment for depression on subsequent cognitive functioning is not well understood.

5.4. Sleep

Several cohort and observational studies link sleep disturbances (for example, insomnia and sleep apnea) to increased risk for cognitive decline [129–137]. A recent study further suggested that treatment for breathing disorders that occur during sleep—specifically with continuous positive airway pressure (CPAP)—may reduce the risk of cognitive decline [134]. However, how the exact nature or duration of an individual's sleep problems are related to increased risk is not well understood, nor is it clear whether the sleep disturbances are a cause of or a related precursor to dementia.

6. A multivariate approach to risk reduction

Recent data from several retrospective studies have found declining dementia prevalence or incidence rates in specific population cohorts since the 1970s [138–142]. Some of these studies have noted the large improvements in educational attainment (including higher rates of graduation from high school and college attendance) among the more recent cohorts [138,139,142], underscoring the existing evidence that formal education is beneficial for reducing an individual's risk for cognitive decline and dementia [62,103–111]. Some studies have also noted that over the same period of declining dementia prevalence or incidence, cohorts of study participants had substantial improvements in management of cardiovascular risk factors as well as considerable declines in smoking, heart disease, and stroke [138–140,142]. This has led to the suggestion that medical and public health interventions to lower various cardiovascular risk factors may have had the additional benefit of improving cognitive health in those specific populations [143,144]. Furthermore, some studies have shown those with multiple vascular issues are at higher risk for cognitive decline and each additional vascular risk factor may be additive to the individual's risk of cognitive decline [145,146].

Given that most of these cardiovascular risk factors are interrelated and connected to the general notion of a healthy lifestyle, focusing on one single lifestyle or health factor may be insufficient to reduce an individual's risk of developing cognitive decline and/or dementia. Some have suggested the most effective strategy may be to address multiple risk factors simultaneously [145,147,148]. The idea of a multivariate approach to reducing risk for cognitive decline was tested in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)—the first published randomized controlled trial on multivariate risk factors and cognitive decline. Recent results from the study, which selected subjects with higher cardiovascular risk profiles, found overall cognitive performance as well as executive function improved significantly with a multi-component lifestyle intervention involving physical activity, nutritional guidance, cognitive training, social activities, and management of cardiovascular risk factors [149].

7. Conclusions

As a result of the Association's review of the current state of evidence on risk factors related to both cognitive decline and dementia, it is clear that there are still many unanswered questions and significant uncertainty with respect to the relationship between individual risk factors and dementia (for example, to what degree there is a causal relationship). There is a clear need for more research on risk reduction, prevention, and brain health—both more longitudinal, population-based cohort studies and randomized controlled trials on the effectiveness of specific interventions that address modifiable risk factors.

However, the Association also believes there is sufficiently strong evidence, from a population-based perspective, to conclude: (1) regular physical activity and management of cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) have been shown to reduce the risk of cognitive decline and may reduce the risk of dementia; and (2) a healthy diet and lifelong learning/cognitive training may also reduce the risk of cognitive decline. The Institute of Medicine, drawing on a panel of distinguished researchers in the field, recently examined the evidence with regard to cognitive aging and cognitive decline and reached a virtually identical conclusion [150].

The evidence has now reached a point that it can no longer remain simply an exercise in academic discussion. The public should know what the science concludes: certain healthy behaviors known to be effective for diabetes,

cardiovascular disease, and cancer are also good for brain health and for reducing the risk of cognitive decline. For our part, the Alzheimer's Association is launching a new brain health education program, *Healthy Habits for a Healthier You*. It is designed to provide consumers with the latest research and practical information on ways they can take care of their bodies and brains to age as well as possible.

For maximum impact, a broader effort must be undertaken—and governments must be involved—to increase public awareness and education about known and potentially modifiable risk factors of cognitive decline and dementia. Since the Association presented its conclusions, the WDC issued a statement encouraging all nations not only to invest in further research, but also to incorporate dementia risk reduction and management into public health policies, public health campaigns, and non-communicable disease strategies and action plans [151]. It is a two-pronged approach: promote risk reduction today based on the scientific evidence available and pursue more research so the evidence will be stronger and more definitive tomorrow.

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