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

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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.

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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].