Effects of Lifestyle Factors on Cognitive Resilience: Commentary on “What This Sunny, Religious Town in California Teaches Us About Living Longer”

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Recent media reporting on healthy living and longevity highlights the ever-increasing public interest on the effects of lifestyle choices on disease risk. The recent CNN article “What this sunny, religious town in California teaches us about living longer” by LaMotte and previous media reports have featured stories about the city of Loma Linda in California, one of the five original “blue zones” in the world, areas or populations with documented high longevity. Loma Linda was labeled as a “blue zone” based upon research conducted at Loma Linda University on long-lived Seventh-day Adventist populations, as detailed below. A majority of the people in Loma Linda belong to the Seventh-day Adventist faith, which advocates healthy living and a life of service. This lifestyle encourages a vegetarian diet, exercise, reducing stress, promoting social connections, and the practice of faith, which is at the core of

the Adventist community. The vast majorities of Adventists are non-smokers and avoid alcohol, and many follow a predominantly vegetarian dietary pattern. Furthermore, most have a high educational background and are dedicated to community service [1]. Adventists have a higher life expectancy than their peers, with females living 4.4 years and males 7.3 years longer on average when compared with the general California population [2]. Therefore, Adventists have been the focus of numerous epidemiological studies examining the relationship between healthy living and health outcomes.

Three long-term studies focused on this population have explored the effects of lifestyle and diet on disease outcomes. The earliest major study of the Adventists began in 1958, referred to as the Adventist Mortality Study [3]. This was followed by the Adventist Health Study 1 (AHS-1) in 1974, which studied the association between diet and various diseases including cancer and cardiovascular disorders. Subsequently, the National Cancer Institute funded the Adventist Health Study 2 (AHS-2) to investigate associations of diet and other lifestyle factors with cancer risk and metabolic indicators for disease [1]. The AHS-2 study enrolled approximately 96,000 cohort members throughout the USA and Canada between 2002 and 2007, and included a high proportion of vegetarian (or near vegetarian) participants (~50%) with a mean age of 57 years during enrollment [4]. Approximately, 27% of the participants are Blacks/African Americans, and 65% of the subjects are women [4]. These studies examined the risk of chronic health conditions such as cardiovascular disease, cancers, and diabetes, and found the incidence of these diseases to be lower in Adventists compared with the general population [1, 5]. Furthermore, a healthy lifestyle and vegetarian diet had a negative association with mortality, thus increasing longevity [2, 6]. The relationship between diet and several health outcomes was also examined in the AHS-2 cohort, showing multiple health benefits associated with a vegetarian diet. For example, the risk of

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colon cancer and coronary heart disease increased with meat consumption, and the risk of coronary heart disease decreased with nut consumption [7–9]. Vegetarian dietary patterns were also associated with improved health outcomes including lower body mass index, and a lower prevalence of adverse health conditions such as diabetes mellitus, metabolic syndrome, and hypertension as well as lower all-cause mortality [4]. These findings are consistent with other studies on the effects of vegetarian diets on health [10, 11].

Norton et al. and Livingston et al. estimated that about a third of Alzheimer's disease (AD) cases worldwide may be attributable to potentially modifiable risk factors [12, 13]. Additionally, a systematic review of epidemiological studies of dementia conferred by stroke found that the risk of incident dementia was doubled in the older population with a history of stroke compared with those without stroke [14]. Findings from Adventist Health studies provide evidence that various modifiable risk factors for stroke including chronic health conditions such as cardiovascular disorders, diabetes, coronary heart disease, and hypertension are lower in the Adventist cohort, which is highly relevant given that stroke patients have increased risk of developing dementia [14]. Furthermore, population-based studies show that various modifiable risk factors in midlife, especially Western dietary patterns, physical inactivity, and poorly controlled cardiometabolic factors such as hypertension, obesity, and diabetes are associated with a higher risk of cognitive decline, including dementia onset [15]. Research efforts focusing on the AHS-2 cohort have the potential to systematically examine the relationship between modifiable lifestyle factors and cognitive health with the goal of identifying lifestyle factors that positively influence neurocognitive performance.

Alzheimer's disease is an urgent public health problem, with the number of cases worldwide expected to increase from 30.8 million in 2010 to 66 million by 2030 and 131 million by 2050 [12]. Reducing the prevalence of each risk factor by 10% or 20% per decade could substantially decrease the worldwide prevalence of AD in 2050 by 8–15%, which translates to between 8.8 million and 16.2 million cases avoided [12, 13]. Emerging evidence shows the beneficial effects of lifestyle interventions, such as those practiced by Adventists, on cognitive outcomes [13, 16]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was the first large-scale long-term randomized controlled trial to assess the effects of a 2-year multidomain lifestyle intervention to prevent cognitive decline in at-risk elderly people (60–77 years) from the general population [17]. Lifestyle interventions including diet, physical exercise, cognitive training, and management of vascular risk factors improved or maintained cognitive function in at-risk elderly people after 24 months [17]. A meta-analysis on the effects of exercise training on cognition found that aerobic exercise may improve neurocognitive performance and that physical activity may enhance memory in individuals with mild cognitive

impairment [18]. Exercise-induced structural and functional changes in the brain including increased total brain and hippocampal volume, improved cerebral blood flow, and increased gray and white matter integrity were observed, along with improvements in cardiorespiratory fitness [19, 20]. While cognitive benefits of physical activity vary considerably across individuals, it has become increasingly clear that such activity reduces AD risk [16]. A Western diet high in red/processed meat, fatty foods, refined grains, and sugar has been associated with cognitive decline [21], whereas Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets are associated with lower risk of AD and rate of cognitive decline [22]. There is also evidence for a role of caloric restriction and intermittent fasting in preventing cognitive decline in elderly adults [23, 24].

Since studies to date on modifiable risk factors in cognitive decline with aging are highly variable with respect to the participants' ages, cognitive status, lifestyle, and existing co-morbidities, further studies are needed on more homogeneous populations to decipher the relationship between modifiable risk factors and age-related development of cognitive impairment. The Adventists are a unique, health-oriented population that may serve as the ideal cohort in which to study the effects of modifiable lifestyle factors such as diet, physical activity, and stress on cognitive outcomes, given the high adherence to plant-based dietary patterns and that two major potential confounding factors—smoking and alcohol use—are largely absent. One study focused on this cohort that examined the incidence of dementia related to the intake of animal products observed a trend towards delayed onset of dementia in vegetarians. Matched subjects who ate meat and fish were more than twice as likely to develop dementia compared with their vegetarian counterparts, although there was no difference in incidence of dementia among unmatched subjects [25]. How do modifiable lifestyle factors create resilience against the development of cognitive decline and neurodegenerative changes in the brain of those at risk of developing dementia, the most common form of which is AD? Lifestyle risk factors are potentially modifiable, and the Adventists have adopted a lifestyle that targets multiple risk factors simultaneously by promoting a living whole healthy lifestyle practice. Therefore, this unique population cohort provides the opportunity to study how lifestyle factors can affect brain aging and AD risk in a healthy population cohort.

We propose that modifiable lifestyle factors such as diet, physical activity, and stress affect resilience against cognitive decline in the elderly population at high risk of AD through modification of biological aging and changes in biological pathways. We propose to evaluate the influence of diet, physical activity, and stress on cognitive retention and brain morphological changes in elderly individuals from the AHS-2 cohort who are at increased risk of Alzheimer's disease due to genetic (i.e., ApoE4 and PSEN1/2) and environmental (such as adverse childhood experiences)

factors. There is evidence of an adverse role in the brain for inflammation, dysregulated metabolism reflected by insulin resistance, and impaired adaptive stress responses in precipitating cognitive decline associated with aging [26] and AD [27, 28]. Thus, molecular mechanisms underlying lifestyle and genetic influences on these adverse factors in cognitive decline should be examined, focusing on their signaling pathways and comparing the rate of biological aging between individuals who maintain cognitive function and those that experience cognitive loss.

Consistent with a study on individuals resistant to cognitive consequences of AD pathology, we predict that levels of pro- and anti-inflammatory compounds differ in these two groups since we have previously shown that AHS-2 vegetarians display a higher abundance of anti-inflammatory, diet-related compounds associated with prevention of cancer and chronic diseases, including urinary polyphenols (isoflavones and enterolactone), plasma carotenoids, and total adipose omega-3 [29], but lower serum concentrations of the pro-inflammatory cytokines, C-reactive protein, and interleukin-6 relative to non-vegetarians [30]. Vegetarians in the AHS-2 cohort also have lower fasting levels of insulin and insulin-like growth factor 1 (unpublished data). Consistent with this idea, it has been shown that systemic insulin resistance is associated with animal protein intake [23] and is inversely associated with adipose tissue alpha-linolenic acid, high levels of which are found in the AHS-2 population [24].

Dietary factors also influence the effect of stress on cognitive decline. Diets characterized by high intake of animal proteins, saturated fats, and refined sugar along with low intake of plant-based foods can increase secretion of corticosteroids, mainly cortisol in humans, a biomarker of stress, which promotes the development of AD [31]. It is possible, then, that there is an array of differences between dietary groups in biomarkers of inflammation, insulin signaling, and stress associated with cognitive health in aging.

Cerebrovascular disease and stroke have been implicated in the development of dementia although the mechanism for cognitive decline is not fully understood [32]. Preclinical studies suggest that ischemia-induced overexpression of amyloid precursor proteins and increased deposition of amyloid β within the brain parenchyma and cerebral vessels contribute to the progression of cognitive impairment in post-ischemic brain [32, 33]. Impaired perivascular drainage of amyloid β has been associated with aging and AD as well as with ischemic and hemorrhagic stroke, which could be a possible mechanism linking stroke with the development of dementia [32]. Additionally, cerebral hypoperfusion, neuroinflammation, oxidative stress, and abnormal expression of amyloid β and tau proteins are common pathophysiological changes encountered in stroke and AD [34], which warrants further exploration to understand the link between the two potentially inter-related conditions. It is imperative that preclinical studies using stroke models follow translational stroke research

guidelines and include aged animals, gender analysis, long-term cognitive evaluation, and examine co-morbidities in stroke research [35], which may elucidate the relationship with dementia and AD.

Lastly, radiological and pathological analyses of brain tissues should examine the differences in morphological characteristics and metabolic pathways in individuals with and without cognitive impairment, focusing on those who retain cognitive function despite the presence of pathological features. These critical studies would potentially shed light on how and why some individuals successfully retain cognitive function despite increased risk of cognitive decline due to genetic, environmental, and/or pathological risk factors.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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