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Review Article

Influence of Lifestyle on Neurocognitive Aspects of Brain Functions and Dementia: Lessons from the Blue Zones

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Abstract

Blue Zones, regions identified for their remarkable longevity and exceptional health, have got attention recently for their potential role in reducing the risk of neurocognitive disorders such as dementia. This paper explores into the lifestyle practices within Blue Zones-Okinawa, Japan; Ikaria, Greece; Nicoya, Costa Rica; the Barbagia region of Sardinia, Italy; and the Seventh-day Adventist community in Loma Linda, California-and their potential implications for prevention of dementia. This literature review focuses on the specific characteristics of each Blue Zone and their potential influences on cognitive health, considering dietary patterns, social connections, physical activity, and stress management. The analysis integrates a range of factors influencing dementia, including diet composition, social interaction, physical exercise, and stress reduction. It discusses how adherence to the "Power 9" principles, encompassing a plant-centric diet, social engagement, and regular physical activity, may potentially mitigate risk of dementia by modulating inflammation, improving vascular health, and enhancing cognitive function. This paper underscores the necessity for further empirical research to establish a concrete link between the "Power 9" principles and the prevention of chronic neurocognitive disorders. This manuscript emphasizes the need for further exploration and potential adoption of lifestyle elements from Blue Zones as a foundation for global cognitive health promotion and the development of innovative strategies for dementia prevention.

Keywords: *Blue Zones; Power 9; Dementia Prevention; Neurocognitive Aspects*

Introduction

"Blue Zones", specific regions around the world where individuals exhibit prolonged and healthier lives compared to the global average, have garnered significant attention from researchers seeking to understand the key determinants of longevity. Initially brought to prominence by Dan Buettner through his article "The Secrets of Living Longer" and the documentary "How to Live to 100" on Netflix, these regions include Okinawa, Japan, Ikaria, Greece, Nicoya, Costa Rica, the Barbagia region of Sardinia, Italy, and the Seventh-day Adventist community in Loma Linda, California [1].

Studies in these areas have underscored nine predominant factors, referred to as the "Power 9", believed to play pivotal roles in fostering longevity. These factors encompass lifestyle practices such as natural movement patterns, a sense of purpose, effective stress management, adherence to the 80% rule of eating, a flexitarian diet, moderate wine consumption, social connectivity within a supportive community, prioritization of familial relationships, and a profound sense of belonging [1].

In the context of these regions, inhabitants engage in physical activities integrated into their daily routines, therefore eliminating the need for gym membership. Furthermore, the residents demonstrate a keen sense of purpose guiding their actions, influenced, for instance, by religious faith in the case of the Loma Linda community. The practice of 'Down Shift' pertains to established strategies for stress reduction, exhibited by communal gatherings over meals and wine in Sardinia, and the moderation of food intake, with individuals in Okinawa adhering to the principle of stopping at 80% fullness while consuming flexitarian diet, as seen across all these regions. Likewise, the communities display robust social networks characterized by familial cohabitation, close-knit friendships, and shared religious affiliations, fostering a sense of brotherhood. Despite the benefits of the "Power 9", there is limited empirical data exploring the relationship between these practices and the prevention of dementia in these regions [1].

Dementia, characterized by cognitive decline accompanied by memory impairment and compromised daily functioning, presents a substantial challenge among aging populations worldwide, with projections indicating a surge in its prevalence, including Alzheimer's disease [2]. Notably, these Blue Zone regions have been associated with higher quality of life even in advanced age with claims of a lower incidence of hypertension, diabetes, and dementia [3]. Nevertheless, existing research data examining the prevalence of dementia in these regions and the specific factors contributing to this trend remain scarce.

Dementia

Dementia has a significant impact on individuals living with the condition, their families, and communities. Cognitive impairment and dementia are categorized as neurocognitive disorders [4]. Mild cognitive impairment (MCI) is mainly used to describe transition between normal ageing and dementia. Dementia is characterized by one's deficits in cognitive abilities that may be associated with lack of one's functional decline [5]. It predominantly affects older adults; it is the seventh leading cause of death, and a primary cause of dependency and disability globally [6]. Social and economic consequences have contributed to challenges within societies and care systems as dementia is resulting in an increased threat to global health [7]. For people ≥ 60 years, the global prevalence rates range from 5% to 7%; however, an exponential increase with age accounts for an estimated 20% of people ≥ 85 years displaying evidence of dementia [8]. Moreover, in 2019, an estimated amount of 55.2 million people worldwide was recorded as living with dementia; this number is expected to increase to 152 million by 2050 [6]. Presently, this accounts for a substantial total global cost of $1313 billion. Initially, 74% of this cost was due to dementia in high-income countries while 61% in low- and medium-income countries. However, a significant increase of 62% was recorded between 2010 to 2019, where there was a skew in the distribution of cost from high-income countries to low- and medium-income households. In the low-and-medium income countries, the increase in the aging population and the higher estimates of informal care were attributable to the shift of increase incidence of dementia [6]. Consequently, countries with low-and medium income households may also be subjected to higher financial burden due to the higher rate of people living with dementia.

Risk factors contribute to increased incidence of dementia. These include lack or decreased education in early life, hypertension, obesity, hearing loss, traumatic brain injury, and alcohol misuse in midlife and smoking, depression, physical inactivity, social isolation, diabetes, hyperlipidemia, and air pollution later in life [9]. Additional factors that pose as risk are hyperhomocysteinaemia, carotid artery disease, post-traumatic stress disorder and prolonged use of anticholinergic medication [10]. Based on recent supporting data, the initial major proven risk factor of age may be declining due to improvement in medical and lifestyle factors [11]. This is especially evident in the centenarians living in the blue zones, who have aged well beyond 65 years and possess a high quality of life, with reduced presentation of neuropathological disorders. Conversely, factors that reduce neuropathological damage and increase and maintain cognitive reserve reduce the risk of developing dementia. These factors include minimizing diabetes, treating hypertension, preventing head injuries, cessation of smoking, reduced air pollution, reduced midlife obesity, maintaining frequent exercise, reducing occurrences of depression, avoiding excessive alcohol use, treating hearing impairment, maintaining social engagement, and high levels of education [12].

Dementia in Blue Zone

Analysis of dementia in Ikaria vs. rest of Greece

Neurocognitive health of Ikarians are indicative of the impact of their modifiable lifestyle choices. Those over 90 years old demonstrate strong family support, social interactions, and increased physical activity. In fact, Legrand., *et al*. reported that among 71 participants, 77.9% partook daily social contacts and 71.8% of participants engaged in moderate to high levels of physical activity [4]. Additionally, the level of adherence to the Mediterranean diet is indicative for the overall outcome. According to the Hellenic Longitudinal Investigation of Ageing and Diet study, each unit increase in the Mediterranean dietary score was associated with a 10% decrease in the odds for dementia. Adherence to the Mediterranean diet was also associated with better performance in memory, language, visuospatial perception, and the composite cognitive score; the associations were strongest for memory. Fish consumption was inversely related with dementia, and cognitive performance was positively associated with non-refined cereal consumption. This is because of the association of the Mediterranean diet and lower level of inflammatory markers including C-reactive protein and interleukins [13]. These markers increase the risk of Alzheimer's disease and vascular dementia. The study suggests that it's the overall diet pattern, rather than specific foods, that provides protection against cognitive decline.

A HELIAD (The Hellenic Longitudinal Investigation of Aging and Diet) study compared two regions in Greece investigated the APO-ε4 alleles and found that carrying at least one APOE-ε4 allele predisposed to dementia. The presence of two alleles resulted in a 12-fold risk of Alzheimer's disease. The study also noted that there is a latitudinal gradient for the presence of the APOE-ε4 allele, with its frequency decreasing as one moves from northern to southern countries in Europe, whereas the opposite is true for the ε3 allele, the neutral variant [14]. These findings suggest that Ikaria may have a lower frequency of the genetic risk factor responsible for dementia, as opposed to its northern counterparts.

Analysis of dementia in Sardinia vs. rest of Italy

Sardinians have notable protective factors when compared to the rest of the Italian population. Centenarian from Sardinia self-report lower levels of depression and overall higher psychological well-being, indicating better quality of mental health. Research conducted in the Sardinian Blue Zone indicates that having strong dispositional resilience can lower the risk of dementia [15]. The study, which involved 160 older adults from the Blue Zone, found a connection between trait resilience and key indicators of mental health. Those with higher trait resilience reported fewer depressive symptoms and higher psychological well-being. It's worth noting that gender differences were identified, with males displaying notably higher trait resilience. The study's regression analyses emphasized the significance of dispositional resilience and satisfaction with social ties as crucial factors in predicting overall mental health, suggesting that these aspects contribute significantly to the impressive mental well-being observed in older adults from the Sardinian Blue Zone [15]. Other key feature leading to successful ageing is contributed to the enhanced social support system, strong relationships with family and friends and increased leisure activities [20]. All these psychological and social aspects are common but important themes that lead to a more relaxed lifestyle, decreasing the risk for dementia.

In Sardinia's Longevity Blue Zone (LBZ), a nutrition transition in the mid-1950s, has contributed to remarkable longevity. Despite economic development, the LBZ has continued to adhered to a traditional diet, characterized by cereal-derived foods and dairy products, a practice that endures among a significant portion of the population [16]. It is interesting to note that while Sardinians' Mediterranean diet is shared amongst other neighboring countries, it is the preservation of antique foods still present in their diet that may play a role in their longevity and potentially their neurocognitive outcomes. Sardinian genetic traits directly trace back to Neolithic-era Nuragic ancestors due to the island's isolation. Unique "famine foods," such as acorn bread with clay and worm-infused soft cheese have emerged as local

delicacies [17]. This in combination with a higher percentage of antioxidant foods contribute to lower incidence of neurodegenerative diseases.

Analysis of dementia in Okinawa vs. rest of Japan

Japan, with the highest proportion of elderly population globally, faces the challenge of a projected surge in the prevalence of dementia. Present estimates suggest a national prevalence rate ranging between 10% to 15% [18]. Notably, the Hisayama study revealed a striking lifetime risk of dementia exceeding 50% among the elderly population [19]. Numerous scholarly publications attribute the increasing prevalence of dementia to the increase in life expectancy and the implementation of early detection methodologies [20]. Earlier investigations found a higher incidence of vascular dementia in contrast to Alzheimer's disease within Japan, as opposed to Western nations [21]. Nevertheless, recent research indicates a shift in this pattern, pointing towards a more frequent occurrence of Alzheimer's disease over vascular dementia [22].

Okinawa, a secluded prefecture situated within the boundaries of Japan, boasts highest prevalence of centenarians, measuring at 54.37 per 100,000 individuals [23]. A study conducted in 1991 evaluating the prevalence of dementia in Okinawa indicated a rate of 7.3, while a subsequent investigation in 1995 suggested a decreased prevalence of 6.7% [22]. Notably, an examination focusing on the 90 to 99-year-old cohort, within the 1995 study, revealed an elevated prevalence of 41.4% among women and 21.2% among men [24]. Both studies collectively highlight the distinctive characteristic of a relatively lower prevalence of dementia in Okinawa as compared to the national average prevalent across Japan.

In 2002, researchers compared the results of the 1991 for Okinawa to Okinawan immigrants living in Brazil. They discovered a prevalence rate of dementia of 12.1% with 47.3% accredited to Alzheimer's and 5.2% to vascular dementia [22]. The elevated rate of dementia in the Japanese Brazilians is attributed to the lower consumption of fish [25]. Omega-3 polyunsaturated fatty acids (n-3 PUFA), found in fish, have anti-inflammatory properties and protective effects against cardiovascular disease and cognitive decline [26]. Subsequent research on the relationship between n-3 PUFA and cognitive function in the dementia-free 80 years and older population in Japan, part of the Keys to Optimal Cognitive Aging Project, specifically focused docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Lower serum levels of DHA and higher serum levels of EPA were associated with improved cognitive function. Participants with higher levels of EPA scored 2.38 times higher on the Japanese version of the Mini-Metal State Examination while those with lower EPA levels had lower cognitive function [27]. Similarly, the Three-City Study in Bordeaux found that higher serum EPA was associated with a lower incidence of dementia of all types [28].

Analysis of dementia in Nicoya Peninsula vs. rest of Costa Rica

Costa Rica, a middle-income developing country, provides free medical examinations to individuals aged 65 and older, with approximately two-thirds of the population within this demographic availing themselves of this service [29]. The national healthcare program includes diagnostic and therapeutic services targeting the identification and management of dementia. In a pursuit to determine the effectiveness of screening procedures for diverse forms of dementia, such as Parkinson's disease, Alzheimer's disease, and mild cognitive impairment, an investigation was undertaken. Within a cohort of 145 participants, 81 individuals were found to have either Parkinson's, Alzheimer's, or mild cognitive impairment [29]. Subsequent research delving into patient records from the Memory Clinic in Costa Rica, spanning the years 2007 through 2014, unveiled that a63.5% of the 3572 patients assessed met the established criteria for dementia, with 47.1% of these cases corresponding to Alzheimer's. Notably, within the entirety of the dementia-afflicted population, 64.7% were identified as female. Additionally, 10.6% of the patients satisfied the criteria for mild cognitive impairment [30].

Nicoya, Costa Rica, with a population of 326,000 is exhibits a 20% lower mortality rate than the rest of Costa Rica with the inhabitants having lower body mass index, taller height, and decreased prevalence of physical and mental disability [1]. The people of Nicoya

demonstrate reduced calorie intake and decreased red meat consumption. Their diet primarily includes legumes, cereals, fruit, dairy, daily coffee, and a high portion of potatoes [31]. A study suggests dairy consumption serves as a protective factor against dementia and daily intake of coffee reduces the risk of Alzheimer's and Parkinson's disease. Despite being costal, locally bred pork and beef were consumed more than fish [31]. The red meat consumption protects against excessive muscle mass loss in the elderly population. Interestingly, a sample of Nicoya inhabitants found an average of years of formal education for females to be 3.1 ± 2.6 and 3.5 ± 2.9 for males despite higher levels of education serving as a protective factor against dementia [31].

Additionally, the inhabitants of Nicoya have longer leukocyte telomere length (LTL) than other Costa Ricans, supporting previous research associating longer LTL with longer lifespan [32]. In contrast to findings in industrialized nations, lower socioeconomic standing correlated with 105 base pairs increase of LTL [33]. LTL is associated with total cerebral gray matter and white matter volume, particularly in the parietal and temporal regions [34]. The longer the LTL, the greater the hippocampi volume [35]. The shortening of LTL is associated with normal aging; however, inflammation, oxidative stress, cardiovascular disease, and disease state affect cognition and brain structure can expedite the process [33]. Studies found that a sample population of APOE e4 homozygotes and those with Alzheimer's had shorter LTL [36]. The shortening of LTL precedes cognitive decline and promotes disease state in positive feedback by promoting cellular senescence, apoptosis, and metabolic failure [37]. However, exercise and healthy diets, as in Nicoya, are thought to slow down the shortening of LTLs [38].

In a separate examination focusing on the health status of the centenarian population in Nicoya, one individual out of the 43 participants was diagnosed with Parkinson's disease. In the same study, assessment for cognitive impairment within this cohort revealed that 31 out of 37 participants were suspected of exhibiting cognitive deficits [39]. Overall, the existing dataset pertaining to the prevalence of dementia in Costa Rica, including the specific case of Nicoya, remains limited, thereby posing a challenge in establishing a concrete correlation between the distinctive attributes of the blue zones and the prevalence of dementia.

Analysis of dementia in seventh day adventists in Loma Linda vs. rest of California

Loma Linda, California, is the only blue zone in America. It is home to a Seventh Day Adventist Faith community with a population of over 9000 people. This community outlives the average American by 10 years [1]. Adventists have a higher life expectancy than Californian counterparts; on average, females live 4.4 years and males live 7.3 years longer in comparison to general population of California [40]. The increase in life expectancy is attributed to their healthy living and dedication to community service. The Seventh Day Adventist community in Loma Linda encourages practicing faith, a vegetarian diet, fostering social connections, exercise, and reducing stress. The majority do not smoke and refrain from consuming alcohol. Most have also attained a high educational background [41]. Protective factors related to diet may result from dietary phytochemicals in legumes, vegetables, fruits, and nuts which are consumed instead of animal products [42]. Social and religious factors provide this community with a more impactful social support system, community involvement and access to psychological assistance.

These factors may lead to a reduction in stress and may have an effect on mortality [43]. Emerging evidence have demonstrated how the beneficial effect of the lifestyle adopted by Adventists may also impact outcomes of cognitive functions [44].

The effects of lifestyle and diet on outcomes of diseases for this population were assessed in three long-term studies [45]. The studies were the Adventist Morality Study, which was initiated in 1958, the Adventist Health Study 1 (AHS-1) initiated in 1974, which analyzed the correlation between diet and diseases including cardiovascular disorders and cancer and the Adventist Health Study 2 (AHS-2) which studied the correlation between diet, additional lifestyle factors and cancer risk and metabolic indicators for diseases [46]. Collectively, the risk that's associated with chronic health conditions including cardiovascular disease, cancers, and diabetes was investigated and found that in comparison to the general population, the incidence of these diseases are lower in Adventists [46]. Moreover, findings

demonstrated a negative association between a healthy lifestyle, vegetarian diet and mortality, thereby resulting in increasing longevity [47].

Evidence from Adventist Health studies have shown modifiable risk factors for stroke, such as chronic health conditions, namely, cardiovascular disorders, diabetes, coronary heart disease, and hypertension, which increase the risk of developing dementia, are observed to be lower in the Adventist cohort [48]. However, an increased risk is observed in the Californian counterparts. Population-based studies demonstrate that modifiable risk factors in midlife are associated with higher risk of cognitive decline, including dementia onset [49].

How Power 9 contributes to protective factors against centenarians in the Blue Zones

Although one's genetic background is significant, studies have shown healthier social and behavioral patterns also have profound impact on risk of developing dementia [50]. In the centenarians of Blue Zones, "Power 9" serves as protective factors decreasing the risk of developing conditions which would increase development of dementia. Living a healthy lifestyle and maintaining a vegetarian diet had a negative correlation with mortality, thereby increasing longevity [47]. A study analyzing the incidence of dementia linked to consumption of animal products found a delayed onset of dementia in vegetarians in comparison to matched counterparts that consumed fish and meat. The non-vegetarian matched counterparts were twice as likely to develop dementia compared with their vegetarian counterparts [51].

The Adventist Health Study-2 cohort showed multiple health benefits observed in the relationship between diet and health outcomes that are associated with vegetarian diet. For example, the risk of developing fatal or non-fatal coronary artery disease was decreased by frequent nut consumption [52]. Evidence from another study has also shown a strong association between 'Meat' protein factors and increased risk of mortality due to cardiovascular diseases, whereas 'Nuts and Seeds' are associated with lower risk [52]. The protective factor of nut consumption is attributable to the reported inverse correlation between intake of dietary glutamic acid, the predominant amino acid in plant protein, and blood pressure [53]. Additionally, the high content of L-arginine in the nuts is a precursor to nitric oxide, which plays an essential role in vascular health. Conversely, the amino acid, glycine, may be attributable to the association of meat product consumption and blood pressure [54]. The association of dietary factors and cardiovascular pathologies are important in decreasing risk dementia as another study has demonstrated how managing vascular risk factors, including lowering risk of coronary vascular diseases, have been associated with improving and maintaining cognitive function in at risk elder after 24 months [55]. Lowering the occurrence of cardiometabolic conditions is relevant since several types of dementia are affected by mechanisms or processes that result in other diseases including inflammation, metabolic dysregulation and vascular changes [56].

Western diets composed of high intake of red or processed meat, fatty foods, refined grains, low intake of plant-based foods and refined sugar have been associated with cognitive decline [57]. These foods are associated with increased secretion of corticosteroids, primarily cortisol in humans, which is a biomarker for stress, which enhances the development of dementia [58]. Mediterranean diets are also practiced in the Blue Zones. Mediterranean diets are associated with lower risk of Alzheimer Disease and rate of cognitive decline [57]. Adiposity, resulting in increased BMI, is associated with metabolic syndrome and is a significant risk for diabetes mellitus, cardiovascular diseases, and various cancers. Findings showing the gradual increase in body mass index (BMI) from vegan to non-vegetarians may serve as an intermediate in pathways influenced by dietary pattern and resulting in diseases [59]. Overall, vegetarian diet is associated with improved health outcomes as it lowers BMI and leads to a decreased prevalence of comorbid health conditions including diabetes mellitus, metabolic syndrome, and hypertension. This all results in an all-cause decrease in mortality [59]. These findings were also observed in other studies focused on the effects of vegetarian diets on one's health [60].

Although the cognitive benefits associated with physical activity may differ across individuals, it is evident that it decreases the risk of dementia [44]. A meta-analysis which assessed the effects of exercise training on cognitive function found that aerobic exercise may

assist in improving neurocognitive performance [61]. Exercise induces structural and functional alterations in the brain. This includes an increase in total brain and hippocampal volume, improved blood flow in cerebrum, and increased integrity in the gray and white matter.

Caloric restriction and intermittent fasting were found to also prevent cognitive decline in elderly adults [62]. This is especially observed in the Okinawans, who have adopted a Confucian mantra stating Hara bachi bu, which constitutes the '80% rule'. The Okinawans restrict the consumption of food to only 80% of a full stomach. The caloric restriction results in a decreased ATP:AMP ratio, which activates the AMP-activated protein kinase (AMPK) [63]. Studies have described the significant role of AMPK activation in inhibiting inflammatory responses induced by various stimulating insults [64]. AMPK's anti-inflammatory response is significant as there is evidence that showed an adverse role in the brain for inflammation, dysregulation in metabolism due to insulin resistance, and impairment in adaptive stress responses in progressive cognitive decline that is associated with aging and Alzheimer's disease [65].

Conclusion

Research into Blue Zones and their influence on longevity has revealed numerous aspects encompassed in "Power 9". These are among the basic pillars of well-ageing in those populations, which also have implications for dementia prevention. Dementia is a growing global problem which has multi-facet repercussions on an individual, a family or the socioeconomic development. Increasing incidence of dementia with its economic impact necessitates determining appropriate preventions. The connection between lifestyle decisions and lower neurocognitive disorder rates is evident in the Blue Zones.

Although Blue Zones have low incidence of chronic illnesses and present these as a result of their lifestyle, published data supporting these is limited. Most of the research studies are based on dietary patterns and it has been observed in some cases that the occurrence of chronic diseases is low, but lack of concrete empirical evidence to support it. Thus, more research studies are required to examine the linkages between the "Power 9" principles and diminution of chronic diseases such as dementia in the Blue Zones. Thus, knowledge derived from blue zones is a great start toward the understanding of how we choose a lifestyle that affects our health. Nevertheless, in-depth research of lifestyle elements in different communities is important to confirm and use these findings on a big scale. Closing this knowledge gap may create new avenues for preventing dementia and ensuring good cognitive health around the world.

Author Contributions

All authors contributed to conceptualization, methodology, resources, writing-original draft preparation and writing-review and editing. All authors have read and agree to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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