REVIEW ARTICLE

Lifestyle components of the global oldest old assessed as effective non-pharmacologic strategies to maintain lifelong cognitive and functional health

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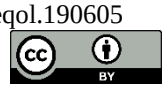

Abstract

Longevity and high quality of life are amongst the most desired traits of humanity. However, the incidences of non-communicable diseases are rising, while sedentary lifestyles and malnutrition are more common than ever, and in general both functional and cognitive health is declining. Besides the concurrent costs to provide healthcare for such an aging population are dramatically increasing and depend on pharmacological treatment. There is an urgent need to raise awareness for cost-saving healthier customs and to adjust lifestyles. From specific geographic areas around the globe, where its citizens tend to grow (very) old, that is over 100 years of age (indicated as 'oldest old'), without the obvious health-deficits, the so-called blue zones, lifestyle factors have been identified, or will be proposed, and taken as candidate for non-pharmacologic approaches to improve general health. This paper will summarize scientific studies focussing on cardiovascular and cognitive health benefits induced by: Physical activity through exercise, light to moderate intensity, and non-exercise outdoors activities; Nutrition through the Mediterranean diet and the incidence of neurodegeneration; Cognitive engagement through cognitive-motor exercises, language usage, and meditation; and finally: Sleep. The identified denominators are reviewed through various scientific studies regarding substantiated health-inducing effects. Adherence to such non-pharmacologic lifestyles is eventually a personal choice, and for governments to take notice of, and to include in policies.

Keywords bilingualism • cognition • dementia • sleep • vitamin D • yoga.

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Introduction

Several geographical regions in the world have gained attention since their inhabitants grow older and stay healthier than in any other place in the world. These regions, identified by a remarkably high density of healthy and physically fit centenarians (indicated as 'oldest old'), are designated blue zones (Buettner & Skemp, 2016). The regions are distributed throughout the world: Sardinia in Italy; Okinawa in Japan; Loma Linda in California, USA; Nicoya in Costa Rica; and Ikaria in Greece. They distinguish themselves from other areas around the globe, by embracing lifestyle denominators responsible for longevity and better life quality, identified through anthropological and epidemiologic research analysis (e.g., Fastame et al., 2018; Panagiotakos et al., 2011). The identified denominators are: frequent physical activity incorporated in every-day life through natural movement and agricultural activities; consuming a high-quality sustainable plant-based diet (of moderate portion size) for

which the ingredients are cultivated and prepared for consumption by their own handwork of farming and meal preparation; and daily consumption of a glass of wine. Besides, the inhabitants of these communities are equally-minded, involved in positive social engagement, where meal-sharing and communication are highly appreciated, and family and friends will be taken care of and taken care by. The individuals, through the community and the activities therein, experience a rich sense of purpose to life and take time to relax and to (self)reflect.

In first instance these identified blue zone denominators seem to contradict the habits adopted to in modern Western societies, although many citizens are getting aware of the underlying benefits of these blue zone characteristics. The current paper will identify the scientific equivalents of the blue zone denominators and summarize the associated cognitive and functional health effects induced by these lifestyle factors.

There are crucial reasons to do this, as many of the identified denominators do have a positive cost-benefit ratio, and are of a sustainable character. Thus, another reason for this paper is to direct attention to several of these factors, which can be adhered to by individuals, even in modern Western societies. It will give them the benefit of obtaining higher vitality and quality of health, and simultaneous take care of our environments. Modern western societies might profit from such individual actions.

Physical activity

From the point of view of modern Western-European professional life, a large population of the societies throughout Europe spend their working time in offices, accumulating excessive sitting time, that is, a sedentary and physically-inactive daily routine. This is regardless of meeting the recommended moderate to vigorous physical activity guidelines, like spurts of exercises in gyms during leisure time. In the last decade, some researchers have argued that such combination may be harmful for health (Owen et al., 2010). Among 220,000 Australian adults, more than 11 daily hours of sitting compared with less than four daily hours being physically active, has been shown to increase the all-cause mortality hazard ratio to 1.4 (van der Ploeg et al., 2012). Thus, physical inactivity is becoming a leading risk factor for overall mortality, which is why governments and authorities are promoting physical activity.

Exercise

Plenty of intervention studies with resistance exercise as physical activity improving skeletal and muscular health are available in the scientific literature, but here we want to demonstrate the effect of controlled intervention studies, and summarize the content of relevant systematic reviews and meta-analysis of randomized controlled trials.

Kodama and colleagues identified 25 studies with an average of seven months of intervention, where aerobic training resulted in increases of high-density lipoprotein cholesterol levels, with no association between exercise frequency or intensity (Kodama et al., 2007). 13 randomized controlled trials where physical resistance training was applied on average three times a week for 1.5 to 12 months, compared with a control group and patients with abnormal glucose regulation (Strasser et al., 2010). The physical activity reduced the fat mass and systolic blood pressure, while no statistically significant effects on total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides and diastolic blood pressure were observed. The comparison of 93 trials by Cornelissen and Smart (2013) showed that endurance, dynamic resistance, and isometric resistance training, lowered both systolic and diastolic blood pressures for interventions smaller than six months. Whereas interventions longer than six months induced smaller reductions in blood pressures, and the combination of these types of physical training lowered only diastolic blood pressure. From 29 randomized controlled trials with a median duration of three months, it was shown that exercise significantly improved cardiorespiratory fitness and lowered the levels of fasting insulin, triglycerides and leptin, while increasing the levels of both high-density lipoprotein cholesterol and apolipoprotein A1, and interleukin-18 (Lin et al., 2015).

The effects of exercise physical activity were more pronounced in persons over 50 years of age, men, and persons suffering from type 2 diabetes, hypertension and metabolic syndrome. In general, exercise physical activity directly improves the blood pressure independent on the type of exercise, and positively influences the indicators of metabolic syndrome.

Light to moderate physical activity

The influence of moderate to light intensity physical activity on general health is hardly been investigated in detail, but considering that numerous activities in a

peron's life are of this category, and thus are executed regularly and frequently, it prevents a person from being sedentary. Some recent studies of importance are being considered here.

2,354 middle-aged white adults from the Unites States of America underwent both functional brain scans and carried accelerometers for eight days (Spartano et al., 2019). The results showed that every additional hour of light-intensity physical activity per day was linked to 0.22% greater brain volume, equivalent to approximately a year of less brain aging. This light-intensity physical activity included walking and household activities.

A recent study among 400,000 man and women from the UK studied the likelihood of being depressed while exerting physical activity using Mendelian randomization (Choi et al., 2019). Persons with gene variants believed to increase the likelihood someone will be active, indeed were active, and few of them had experienced depression. Persons without these gene variants, tended to move less, while they also showed greater risks for depression. The ideal amount of exercise to prevent depression started at about fifteen minutes a day of running or other exercise. Walking and household work also protected against depression, but to be effective about an hour a day needed to be performed.

Exercise patterns as described in the previous section are not similar to the physical activity executed in the blue zones. But moderate and light physical activity are more frequently executed in the blue zones. Although limited research is available in this respect, it is worth having a look at research regarding more traditional farming and leisure activities.

Non-exercise outdoors activities

An early paper from the UK showed a higher prevalence of depressive symptoms among farmers (Hounsome et al., 2012). However, factors like climate and environmental changes, financial instability and social isolation were not taken into account. More to the south, a cross-sectional study in Western Greece, among a rural population with a total of 672 farmers of both young and old age, showed that the young farmers had lower prevalence of hypertension, better cognitive health and low depression rates (Demos et al., 2013), while these findings were reversed in older ages. Without the economic burden due to retirement a Japanese cross-sectional study among 1,005 older farmers, showed that farming habits of long duration (more than seven hours per week) significantly lowered the odds ratio for depressive symptoms, as compared to no farming habits (Asai et al., 2018). This positive association held as well for short durations (less than seven hours per week). Additionally, the association was partly mediated by daytime outdoors physical activity, and thus light exposure.

It is likely that the agriculture physical activity, often performed outdoors and thus coinciding with light exposure, secures the activation of vitamin D in the human skin. Deficiency in vitamin D is associated with impaired cognition, which is likely to be linked to loss in plasticity, particularly affecting the hippocampus (Mayne & Burne 2019), a region involved in learning and memory. Thus, securing sufficient serum levels of vitamin D is of crucial importance to human well-being.

Even light-intensity physical activity, like household, agriculture, gardening and walking, can contribute to better health. However, controlled studies among farmers, investigating the association of health with their occupational activities, which often are indicated to be of light to moderate intensity level, are lacking till now. On the other hand, actively engaging in the outdoors environment, especially distant from every-day professional routine, like in nature, gained much interest in the last decade.

A cross-sectional study among 2,079 working adults from the UK, showed that perception of local green space predicted the visit frequency and was positively correlated with reaching recommended levels of physical activity (Flowers et al., 2016). An individual's level of being connected with the natural world has been linked to psychological well-being (Zelenski & Nisbet, 2014). Studies from Japan, but also Europe and the USA, show that performing outdoor walking, gardening or nature viewing, were significantly positively associated with the measured heart rate, blood pressure and various self-reported measures, besides, showed reductions in the experience of stress and improvements of mental health (Hunter et al., 2019; Kondo et al., 2018; Marselle et al., 2019). Thus spending time in outdoors nature environments has positive effects. Walkers as compared to non-walker, showed a reduction in perceived stress, depression, and negative affect, as well as an increase in positive affect and mental well-being (Marselle et al., 2019). Such nature experiences reduced cortisol levels significantly within 20 minutes (Hunter et al., 2019), while an additional 10 minutes, summing up to half an hour, was even more

effective, regardless whether it was spent sitting or walking.

Recent experiments with immersive virtual environments were performed to compare their effect with actual nature walks, and to investigate connectedness to nature and perception of the natural environment. It was shown that nature walks were associated with higher enjoyment and enhanced emotional state as compared to the virtual environment, specifically in relation to a reduction of tiredness and negative affect (Calogiuri et al., 2018). Moreover, from a recent systematic review on nature-based instructions, it was shown that educational time in nature, next to the obvious relief of stress, enhances attention, promotes self-motivation, boosts self-discipline, gives enjoyment and initiates engagement (Kuo et al., 2019), while all these factors improved learning. Besides, outdoors nature education increases physical activity and fitness, to which the leveling up of serum vitamin D levels most likely contributes (Mayne & Burne 2019).

Clearly, a positive respectful relation with the natural environment, with repeated visits, brings mental balance. Both leisure and educational time spent outdoors in nature, promote relaxation and reflection, and is perhaps comparable with the sense of belonging, as practiced in the blue zones.

Nutrition

The diet adhered to by the people of the blue zones, is based on fresh agricultural products, cropped by gardening surrounding lands. The diet is plant-based, predominantly consists out of vegetables, fruits and beans, while meat is added only occasionally, and hence depends on geography and climate.

A healthy diet maintains a healthy balanced intestinal microbiota, and recent research indicates that this symbiosis establishes an intestine-brain axis of major support to the health of the brain (Cryan & Dinan, 2012; Dash et al., 2015; Johnson & Foster, 2018). This axis influences the development of the brain, as well as behavior and mood. Here it is very important to notice that the inclusion of fermented foods, often present in traditional diets, promotes the presence of body-positive microbiota in the intestines (Wen & Duffy, 2017). In the intestines the microbial fermentation of host-indigestible dietary fibers, produces short-chain fatty acids that act as signals in the host (Kelly et al., 2017; Johnson & Foster, 2018). On the other hand, the presence of pesticides and herbicides also influence human physiology (although used little to none in traditional blue zone farming).

Hence the food consumption not only determines the quantity and quality of the micronutrients available to the host, but influences both the symbiosis with microorganisms and the presence of chemical contaminations. Consequently, having effect on the physiology of the host by toxicity, and the microorganism's metabolism and its production of endocrine signals.

Mediterranean diet

A diet widely introduced for a healthier way of consumption – or reducing weight -, is the Mediterranean diet. It too comprises a traditional dietary pattern that is plant-based with freshly-harvested vegetables, fruits, nuts and seeds, beans and legumes, many herbs and spices, and whole grains (e.g., Davis et al., 2015; Katz & Meller, 2014). The diet includes the frequent consumption of fish and other seafoods, but on the other hand promotes selective dairy intake and quite limited consumption of meat, eggs and sweets. It emphasizes the use and consumption of healthful fats like extra virgin olive oils and fish fats. Besides, just like traditionally in the blue zones, both moderation in amount for each of the constituents is promoted, and strikingly, the addition of a few glasses of wine.

Studies on the health effect induced by adherence to the Mediterranean diet are numerously available, with some early systematic reviews (e.g., Serra-Majem et al., 2006; Sofi et al., 2008; Sofi et al., 2010). From 35 experimental studies it was shown that the Mediterranean diet has favourable effects on lipoprotein levels, endothelium-dependent vasodilatation, insulin resistance, metabolic syndrome, antioxidant capacity, myocardial and cardiovascular mortality, and cancer incidence (Serra-Majem et al., 2006). Besides, 18 prospective cohorts running for 3-18 years, showed reduced risk of overall mortality, with a clear reduction of the incidence for cardiovascular, cancer, and neurodegenerative diseases and stroke (Sofi et al., 2008; Sofi et al., 2010). Other confirmed health effects are improved insulin sensitivity, reduced cancer risk, and particularly well demonstrated, the reduced risk of cardiovascular diseases, lower prevalence of general obesity and metabolic syndrome, and also the improvement of quality of life and diminished pulmonary inflammation in asthmatic patients (reviewed by Martinez-Lacoba et al., 2018; Sofi et al., 2014;). Finally, higher adherence to a Mediterranean diet was associated with a reduction in

mortality (Bonaccio et al., 2018; Trichopoulou et al., 2009).

Thus, adherence to the Mediterranean diet, the plant-based diet as described above, seems to provide longevity with a reduced risk for chronic non-communicable diseases. Such non-communicable diseases, including depression and dementia, among people in the blue zones are rare.

Nutrition & neurodegeneration

For Parkinson's disease, a motor-neurodegenerative disorder in which the dopaminergic producing neurons in the brain during a person's life are dying, affecting the person's movement, gait, and balance, it was recently shown that adherence to a Mediterranean diet intervention was associated with a decreased risk of parkinsonism, and with slower progression of parkinsonian signs (Agarwal et al., 2018).

Higher adherence to the Mediterranean diet has been associated with the reduction of the incidence of depression from a meta-analysis among twenty longitudinal and twenty-one cross-sectional studies, as well in four longitudinal studies (Lassale et al., 2018). A recent randomized controlled trial showed that 12-week intervention with a Mediterranean diet significantly reduced the symptoms of major depression (Jacka et al., 2017). In line with these are the results from a systematic review on 11 cohorts (including only one randomized controlled trial), which indicates that higher adherence to Mediterranean diet was associated with improved cognitive function, lower rates of cognitive decline, and reduced risk of Alzheimer's disease (Lourida et al., 2013), and a more recent systematic review that included 25 unique cohorts, five randomized controlled trials and 27 observational studies, confirm these observations (Petersson & Philippou, 2016).

Interestingly, nutritional medicine approaches: adding supplements to the diet and including more proper diets, to persons with chronic non-communicable diseases is gaining attention (e.g., Sarris et al., 2015). And for good reasons, because combined with metabolically enhancing the capacity of Alzheimer's disease patients, it was recently observed to reverse cognitive decline (Bredesen et al., 2016).

Diet and nutrition will become essential future focus points of a person's lifestyle. Especially since climate change and environmental pressure will demand the reduction of energy for food production, transport, and the elimination of food waste. Once persons and societies understand that the food they consume, its micro and macronutrients, but also its contaminations intentionally or unintentionally incorporated in the production process, drastically impact their health, and especially their brain function, behaviour, mood and cognition. Hopefully, more people will demand a larger production of nutrious, high-quality environmental-friendly and sustainable foods in the future.

Cognitive engagement

Peoples in the blue zones are part of likewise-minded small communities, where community-sense, with intensive family and neighbourhood support are practiced. Individuals of such community have purpose, and often practice spiritualism (not necessarily religious), while relaxation within the community setting, in the form of socialising, is a daily routine resulting in the sharing of thoughts foods and drinks. The community and its individuals execute activities through mindful engagement within natural surroundings.

To pursuit such daily activities up till old age, in the absence of age-related falls, health complications and deteriorations, it is likely prolonged exposure to blue zone lifestyle components, requires simultaneous implementation of motor and cognitive tasks. This training then accumulates and brings about, generally fit centenarians who are trained through high-end cognitive engagement. Next, we will discuss several forms of cognitive engagement that can be hypothetically considered a basis for these.

Cognitive-motor exercises

Physical activity, alone or combined with cognitive training can enhance functional fitness in older adults (Paravlić et al., 2016). Simultaneously performing cognitive (e.g., working memory task) and motor (e.g., strength exercises) tasks in elderly are more frequently used for preventing falls. In this way, the individual trains automated execution of simple motions (Ghai et al., 2017). The combination of cognitive-motor exercises has shown to improve attention, control of executive functions, memory and reasoning (reviewed by Bherer, 2015; Lauenroth et al., 2016).

More specific, for example the training of executive functions by computer-based training in sedentary elderly gives rise to improved walking efficiency (Verghese et al., 2010). While computerized spatial-navigation intervention training, emphasizing movement through a virtual

maze, positively influenced both normal and complex walking in healthy elderly men during bed rest (Marušič et al., 2015). The continued spatial navigational testing showed improvements up to four hundred days post-bed rest (Marušič et al., 2018a). Hence it was suggested that such spatial navigation-based computerized training can be protective of detrimental mobility effects. This reflects the potential for cognitive-based training to affect a non-trained domain. Moreover, only to imagine demanding rehabilitation exercises, a specific cognitive function, does influence the process of functional skills as well (Marušič et al., 2018b).

In conclusion, cognitive motor exercises are promising. Although variation is noticed, and study results are even contradicting, the cognitive part can be designed to train various executive functions in combination with physical exercise. Hence, new cognitive-motor exercises will be quite powerful. Such approaches studied and optimized to be effective, will certainly find its way to educational systems and private homes, by delivery in society through entrepreneurs.

Language usage

Another form, less physically active, but more of a cognitive challenge, is the use of language. Especially the use of multiple languages (bilingualism or multilingualism), demands rapid and simultaneous activation of various executive functions, like attention, inhibition, working memory, etc., in a way that the brain performs dual tasks. Being proficient in multiple languages, that is: speaking, reading and writing, has been correlated to enhanced cognition (Bialystok & Poarch, 2014), and to beneficially influence children's cognitive development (Bialystok & Viswanathan, 2009).

Languages learned early on in life, and maintained throughout adult life, establishes bi- or multilingualism, and continually train the brain in a non-conscious way. Especially in older persons, some advantages from such lifelong brain training, seem to emerge in the form of delaying the onset of various neurodegenerative diseases, like dementia. Various cohorts from distinct geographic areas in the Americas and Europe (Alladi et al., 2013; Bialystok et al., 2007; Bialystok et al., 2014; Chertkow et al., 2010; Craik et al., 2010; Gollan et al., 2011; Woumans et al., 2015), entailing about 2,000 participants, showed that the use of two languages, can delay the onset of symptoms of cognitive impairment, the early signs of Alzheimer's disease, with four to five years. Although there is debate about comparable methodology, and some reports have found less convincing evidence, the most striking is that, studies investigating neuroanatomical brain differences between older monolinguals and bilinguals, did show that there is more atrophy among bilinguals (Schweizer et al., 2012). Also, a difference in the brain areas being activated for various tasks is observed (Ansaldo et al., 2015; Gold et al., 2013b), as well as differences in brain tissue integrities are recorded (Gold et al., 2013a; Olson et al., 2015), and different cortical thicknesses (Anderson et al., 2018; Duncan et al., 2018; Olson et al., 2015).

Typically, the bilingual advantage seems to be applicable to other diseases with neuronal damage: like a faster recovery after brain stroke (Alladi et al., 2016), a delay in the onset of frontotemporal dementia (Alladi et al., 2017), and increased frontotemporal grey matter integrity in Huntington's bilingual patients (Martínez-Horta et al., 2018).

Despite the described effects of bilingualism, it has not been thoroughly explored how the use of language, or adding another foreign language to a person's communication proficiency, can affect cognition and executive functioning. Social engagement, trying to understand and communicate another person through language might certainly be part of the basis of cognitive health seen in the blue zones. Bilingualism as a non-pharmacological approach, would be a welcome addition to improving wellbeing or even health in Western societies. Especially since it would support education structures and increase respect for foreign customs and societies.

Meditation

Meditation is a practice that originally combines spiritual attention with physical exercise in the form of body posture and the control of breathing. Depending of its nature, the practice usually demands cognitive and physical mindfulness. For example, yoga originating in India, is now often practiced throughout the Western societies both for health and relaxation.

Recently, participants of yoga classes incorporated as an intervention in randomized controlled studies, showed that yoga from various disciplines has clear advantages as compared to their control groups. Eight to nine weeks of yoga exercises for mood or major depressive disorder patients positively affected depressive symptoms (Vollbehr et al., 2017), and significantly reduced the anxiety symptoms (Sharma et al., 2017). In patients with post-

traumatic stress syndrome, yoga for 6-12 weeks moderately decreased the re-experiencing and hyperarousal symptoms (Mitchell et al., 2014). Along this line schizophrenia patients executing yoga for eight weeks significantly improved their perceived quality of life in the physical and psychologic domains with clear improvements of positive and negative schizophrenia symptoms (Visceglia & Lewis, 2011). Interestingly, for patients with eating disorders one hour of yoga before dinner significantly reduced their pre-meal negative affect. Although the effect was attenuated post-meal (Pacanowski et al., 2017). Despite that these are preliminary studies, the results clearly show some promise, incorporating mindful yoga as a lifestyle for the benefit of general health.

The breathing aspect of yoga has gained a lot of attention recently, and trials with respiratory muscle exercises have been performed. For example, older women with metabolic syndrome undergoing respiratory muscle exercises for seven days (three sets of 15 minutes, with a three-minutes interval), improved both their respiratory and cardiac functions (Feriani et al., 2017). In middle-aged to older adults, six weeks of high-resistance respiratory muscle exercises (thirty breaths per day for six days in the week), the cardiorespiratory fitness was significantly improved, and the exercise time before exhaustion was reached, was prolonged (Heinbockel et al., 2019). The advantages of respiratory muscle exercises are multiple. The threshold to adhere to rigorous breathing exercises is often low, especially as compared to time-consuming aerobic exercise paradigms. Besides, it could be applied to patients with disabilities alongside existing therapies. Thus, respiratory muscle exercises seem to be a practical and promising, modulatory lifestyle factor.

Long term intervention effects of meditation recording biomarkers have also been studied. For example, anxiety disorder patients instructed during an eight-week mindfulness course (yoga, breathing and posture instructions) followed by home-practice intervention, showed a greater reduction in adrenocorticotropic hormone and pro-inflammatory cytokines concentrations, after a social stress test, as compared to control participants (Hoge et al., 2018). Similarly, long-time meditation practitioners compared to non-meditating controls, recovered faster from such cortisol response induced by the same social stress test (Gamaiunova et al., 2019). While the long-term meditation practitioners also reported experiencing less self-conscious emotions after the stressful task.

Thus, it is known that stress is responsible for a variety of negative health outcomes, and it seems that meditation, can initialize to be able to cope better with stress situations, and can minimize typical psychophysiological stress responses. Being part of an equally-minded society, in which one performs meaningful habits, according to certain purposeful routines, might be regarded, at least partly, as a meditation, and can add to quality of life as observed in the blue zones.

Sleep

In general, the inhabitants of the blue zone get sufficient rest (e.g., Pes et al., 2018). Meaning being inactive for an average of 8.5 hours, with an average of 6.3 hours of night-time sleep (Pes et al., 2018). While especially in the warmer and more humid climates, easing down through socializing, and brief daytime naps usually restricted to maximally half an hour, also known as siesta, are very common (Naska et al., 2007; Pes et al., 2018). A meta-analysis showed that deviating a lot more or less from this average night-time sleep duration, increases the all-cause co-morbidity for older adults (Shen et al., 2016). Despite recent understandings of sleep-wake homeostasis, its physiological regulation, and it effect on appetite, energy intake and expenditure (Copinschi et al., 2014), the general public in Western societies does have a wrong impression of sleep and its contribution to general health (Robbins et al., 2019).

Physiological sleep involves several stages characterized by brain activity, that repeat four to six times per night within cycles of about ninety minutes (Copinschi et al., 2014): two stages of light non-rapid eye (REM) movement, are followed by slow-wave sleep (a deeper, non-REM stage), REM sleep, and finally transient awakenings. As the night-time sleep progresses, the number and the duration of the awakenings increase, while the non-REM sleep becomes shallower, and the duration of REM sleep becomes longer, till the final awakening occurs. Intact stages of slow-wave durations often reflect a good quality of sleep (Copinschi et al., 2014), and in elderly persons the durations of the slow-wave and REM stages usually are reduced, leading to an increase of time spent awake.

Various hormones contribute to metabolic homeostasis during sleep. For example, cortisol is produced by the adrenal glands, but production is reduced during sleep especially in the slow-wave stage, giving rise to low circulating cortisol levels during sleep (Charloux et al., 1999). The transient and final awakenings trigger the production of cortisol.

Reducing sleep time and introduction of daytime sleeping, induces overall higher levels of cortisol, which increases the arousal state of the body, usually requesting energy intake. On the other hand, during the slow-wave stages, growth hormone is released while insulin is reduced. These patterns coincide with the reduced use of glucose by the brain and peripheral tissues during the first half of sleep. While glucose demand becomes higher during the night's second half of sleep, that is shallower and more fragmented (Van Cauter & Spiegel 1999).

Leptin, a hormone released from adipocytes, informs the hypothalamus, the brain's metabolic centre, about the energy status of the body. Leptin levels reflect the feeding status of the body, with high circulating levels corresponding to saturation and overfeeding, and low levels correspond to hunger and underfeeding. Sleep time reduction gives rise to lower leptin levels, while enhanced duration of sleep induced a rise of leptin levels (Spiegel et al., 2004a; Spiegel et al., 2004b).

Ghrelin, produced by gastric cells in the stomach wall, also informs the hypothalamus especially indicating hunger, and being a digestion activator. Ghrelin blood levels repeatedly rise during daytime (generally 3 cycles of 3 hours). However, with food consumption the levels drop fast (next 2 hours), before rising again. During the first half of sleep ghrelin levels rise (from last the meal), and decline during the second half of sleep (mirroring cortisol).

The ratio of ghrelin to leptin has been correlated to hunger and appetite and this ratio is a good indicator of energy requirements (Spiegel et al., 2004a; Spiegel et al., 2004b). For example, with sleep extension the ratio declined, showing consistently higher levels of leptin and lower levels of ghrelin (Copinschi et al., 2014), usually favouring energy restriction during daytime. On the other hand, in normal weight persons, during sleep reduction, the ratio of grehlin to leptin increased, inducing enhanced hunger and appetite ratings. Thus, in middle-aged overweight persons, sleep restriction also lead to higher ghrelin to leptin ratio (Nedeltcheva et al., 2010), and induced an increased loss of fat-free body mass, while the resting metabolic rate decreased, and fasting metabolic rate increased, overall negatively influencing energy metabolism.

Under controlled laboratory conditions with healthy participants, limitation of sleep time typically reduced the glucose uptake through reduction of the insulin release (Leproult & Van Cauter 2010; Spiegel et al., 1999; Tasali et al., 2008; Van Cauter & Spiegel 1999). More dramatic responses were observed by specific reduction of the slow-wave stage (Leproult & Van Cauter 2010; Spiegel et al., 1999; Tasali et al., 2008). Thus, both reduction of the sleep time and limited sleep quality give rise to increased risk of type 2 diabetes.

Sleep restriction influences brain activity as well (Greer et al., 2013). Showing decreased activity in cortical regions and enhanced activity in the amygdala. A combination that strongly correlated with increased desires for high-calorie foods and subjective sleepiness. Furthermore, sleep deprivation has been associated with increased levels of anxiety (Pires et al., 2016), and makes us interpret things more negatively (Tamm, 2019). Which all in turn affect general health.

Sleep has been recognized as an important physiologic period of rest, during which, because of the absence of physical activity, the metabolic homeostasis is reset through hormones. However, its contribution to general health is often undervalued in hectic Western societies. This in contradiction to the blue zone communities, where sleep and non-physically active periods of rest, are valued. Research shows that especially the sleep's quality of the slow-wave stages and the duration of the overall sleep, contributes to effective daytime homeostasis, and are crucial for execution of optimal functional and cognitive activities.

Discussion

The present paper reviews several non-pharmacologic approaches to improve general, cardiovascular and cognitive health. These approaches were identified from blue zone denominators, standing out from epidemiologic and demographic research within the areas, were the oldest old can be found to live today. These blue zone lifestyle factors are supposedly good for any person to adhere to, in any habitat, although not always easily to adapt to in Western societies.

The benefits of moving naturally and using natural transportation, perform regular agricultural activities, gardening and household activities, have been identified as light to moderate physical activity, that executed regularly, fights sedentary lifestyles and depression. And while being beneficial to health and psychology, controlled studies show that execution for over an hour produces predominant benefits in the psychological domain, while walking (or sitting) for

half an hour in an outdoors natural environment significantly reduces stress and is positively associated with heart rate and blood pressure, through enhanced enjoyment and emotional state, and reduced tiredness. However, the effects of light to moderate physical activity have been poorly studied.

On the other hand, physical activity in the form of exercise and the Mediterranean diet (that most closely resembles the blue zone nutritional pattern), with long-term adherence to daily fifteen minutes of aerobic exercise (e.g. running), will induce a better health through cardiovascular, cognitive, psychological and functional benefits, reduction of weight, and the risks of hypertension, type 2 diabetes, and metabolic syndrome. In general, they reduce the risk for chronic non-communicable diseases, as confirmed through various studies. The benefits of adherence to a plant-based diet are numerous, as plant-based meals are especially in the long run favoring sustainable food systems. Besides, depending on the scale of cropping and the chemicals introduced, plant-based diets will be more beneficial for the environment and an individual's health. Thus, a plant-based diet seems to reduce depression, fight cognitive decline and dementia, and is beneficial in reducing Parkinson's disease symptoms.

Strikingly many of the blue zone denominators (like agriculture habits and natural transportation), are performed outdoors. While farming habits of several hours per week significantly lowers the risk for depressive symptoms, it also means a person is exposed to fresh air, and receives direct sunlight, boosting the vitamin D levels, that can affect several cognitive functions, like memory and attention, while even affecting schizophrenia in a positive way (Mayne & Burne, 2019). Being outdoors in a natural environment will be beneficial for all ages, brings mental balance, and several studies show that young people will display higher amounts of physical activity, enhance their creativity and fitness. Being educated in nature has the potential of positively enhancing academic performance through multiple factors not fully understood, but the contribution of enhanced attention, self-motivation, and self-discipline, are among them.

Additional blue zone traits have been explored in this review. For example, cognitive-motor exercises, language use and meditation. Although not specifically identified as blue zone traits, the strong societal traits of the blue zones, like a purposeful life, (self)reflection, and appreciated time to relax and sleep, particularly do give some relevance to the weight of meditation. Adherence to various degrees of yoga or mindfulness exercises for several weeks can induce benefits in the form of better coping with stress factors, while improving both respiratory and cardiac functions. Effective for patients with major depression, post-traumatic stress syndrome, schizophrenia and eating disorders.

It is presumed that blue zone inhabitants, will perform dual-tasks, being cognitively busy while performing light physical activity. This would benefit the domains of attention, memory and reasoning, while for elderly especially, would improve their mobility through improved walking skills and fall prevention. Blue zone inhabitants' social time-sharing periods, conversation and meal-sharing, during rest periods, add to their purpose in life and the maintenance of social communication. Understanding your neighbors, friends and family, requires communication, and in a sense demands psychologic interpretation of the limited verbal expression of anyone's mental thoughts. Lifelong multilingualism, in which communication through languages, can benefit cognition in general, and delay the symptoms of cognitive decline with as much as five years. As the incidence of neurodegenerative diseases in blue zones is very low, as compared to modern Western societies, this review included the issues of bilingualism and dementia.

Pes and colleagues notice that the duration of sleep for Sardinian elderly exceeds 82% and 77% of the resting time in the men and women respectively, while adhering to the other blue zone denominators, and maintain excellent physical functionality indexes (Pes et al., 2018). Therefore, sleep physiology research was recapitalized and emphasized, and its crucial role for general health was explained. Sufficient quality sleep is essential to maintain a healthy physiology. Moreover, crucial deviations, especially long-term, can drastically impact the psychological domain of individuals, influence metabolic and caloric states, hence, change body weight, cognition and functionality (increasing the risks for both type 2 diabetes and obesity).

Conclusions

Diet and exercise as effective lifestyle paradigms are taken up in various health promotion programmes at national levels throughout Europe, with resistance exercise an established denominator to maintain skeletal and muscular health. However, the purpose

of this paper was to identify denominators to additionally improve cardiovascular and cognitive health, like gardening, agricultural physical activity, sleep and relaxation in the form of meditation that deserve attention as well, but could be scientifically researched in more detail. Combined with cognitive brain training (for elderly), in the form of cognitive-motor exercises and promoting the use of multiple languages, these non-pharmacologic approaches, in general, can add to a healthy brain, longer lifespan and happier lives. Hopefully this paper contributes to the development and promotion of these denominators.

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