Diet and longevity in the Blue Zones: a set-and-forget issue?

Giovanni Mario Pes[a,b,1], Maria Pina Dore[a,c,1], Fotini Tsofliou[d,e], Michel Poulain[f,g]

[a]Department of Medical, Surgical and Experimental Sciences, University of Sassari, Italy

[b]Sardinia Longevity Blue Zone Observatory, Ogliastra, Italy

[c]Baylor College of Medicine, One Baylor Plaza, Houston, USA

[d]Department of Rehabilitation and Sport Sciences, Faculty of Health & Social Sciences, Bournemouth University, Bournemouth BH8 8GP, UK

[e]Centre for Midwifery, Maternal & Perinatal Health, Faculty of Health & Social Sciences, Bournemouth University, Bournemouth BH1 3LT, UK

[f]IACCHOS Université catholique de Louvain, Louvain-la-Neuve, Belgium

[g]Estonian Institute for Population Studies, Tallinn University, Tallinn, Estonia

[1]Giovanni Mario Pes and Maria Pina Dore contributed equally as co-first authors

***Corresponding author at**: Dipartimento di Scienze Mediche, Chirurgiche e Sperimentali, Università di Sassari, 07100 Sassari, Italy

E-mail addresses: gmpes@uniss.it (G.M. Pes)

Abstract

The Blue Zones (BZs) are areas of the globe inhabited by exceptionally long-lived populations. They include the island of Okinawa in Japan, the island of Ikaria in Greece, the mountain area of the Sardinia Island, and the peninsula of Nicoya in Costa Rica. Their longevity is a relatively recent phenomenon that has been progressively investigated since the dawn of this century. Research efforts over the past two decades have sought to shed light on the factors associated with this longevity, as well as explore the possibility of lessons transferable to the general population. Among the features of BZ inhabitants, described in the literature, their eating habits hold a prominent place, as these have the advantage of being easily quantifiable and applicable on a larger scale. However, it is too often taken for granted that the mere fact of being documented in a long-lived population makes the diet a causal factor of its longevity; this is a claim which should be adequately proven. Furthermore, it is implicitly assumed that a specific BZ diet is homogeneous and remains stable over time, whereas some evidence suggests the opposite. Therefore, this review summarizes our current knowledge of the BZ diets and discusses whether they can be considered as a paradigmatic example of healthy nutrition valid for anyone or rather a set of evolving food patterns that has offered benefits to a few specific communities in recent decades.

Keywords: Blue Zones; longevity; Mediterranean diet; Okinawa; Ikaria; Sardinia; Nicoya

1. Introduction

Eating habits occupy a prominent place among the factors believed to affect one's lifespan. In the popular literature –also frequently in the scientific kind– a particular interest can be found for specific foods, claimed to improve the health of their consumers and preserve their functional capacity into advanced age [1-3]. More recently, the interest of researchers has shifted from the potential impact on the aging process of individual food components to broader food patterns [4]. In reality, these investigations are inherently difficult to conduct in humans, as adherence to a diet cannot be tested under the same controlled conditions as in animal models, and information about the long-term effects of a diet is limited by the short follow-up period allowed with humans [5]. Therefore, most studies are merely observational with the limitations inherent in this study design. The identification of the Blue Zones (BZs), areas of the globe populated by centenarians, provided a

new model to test the relationship between dietary habits and health and longevity. Unfortunately, the idea that the longevity of a population stems from what is being eaten, is often assumed *a priori* without providing convincing evidence. Another bias often found in the literature is the presumption that the diet of a long-lived population is something innate and stable, while our observations of real BZ communities suggest that their food culture is quite heterogeneous and can be traced back to multiple different historical influences. Ignoring these aspects carries the risk of misunderstanding the relationship between dietary patterns and health outcomes at the population level. The four long-lived populations, identified around the world so far reside in: (i) Okinawa, the southernmost island of Japan; (ii) the island of Ikaria in Greece; (iii) an area that includes the mountainous part of Sardinia, Italy; and (iv) an area corresponding to the Nicoya Peninsula in Costa Rica [6-10]. Additional populations with a high prevalence of long-lived individuals have been claimed to deserve the Blue Zone status [11, 12], but no rigorous age validation processes using death certificates and social security records have been conducted in these areas as in the four BZs mentioned above. Analysis of the dietary habits of these communities has been carried out in a non-systematic and incomplete way so far and thus it presents major challenges. The scant literature highlights a great diversity between the diets of the various BZs as well as their variation over time, making it difficult to find a common denominator that can be reasonably extended to all of them and adapted as a model for our post-modern societies. By comparing the diets of the four BZs, some evidence can be found indicating a link between a few typical foods or eating styles and healthy aging. Nonetheless, such comparison also demonstrates that a diet suitable for a specific population may not suit the lifestyle features of another. These issues should be considered with great caution before recommending the adoption of a BZ diet to the population at large.

2. Methods

The international literature on the Blue Zones is not very extensive as the term was first used as recently as in 2004 [7]. The database search strategy of this narrative review spans from that date to the present. More specifically, the search terms “Blue Zones”, “Longevity Blue Zones”, “long-lived populations”, and “population longevity” were entered in databases such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Scopus (http://www.scopus.com/home.uri), Web of Science (http://www.webofscience.com) and Google Scholar (http://scholar.google.com/) to cover grey literature given the fact that BZs are a niche topic. Articles or chapters containing descriptions of dietary habits in any of the four Blue Zones written in English, Italian, Greek or Japanese were selected. An initial reference list was based on title and abstract screening, followed by full-text

reading of potentially relevant sources of information about Blue Zone diets. The final reference list was prepared through discussion between all co-authors.

3. Okinawa BZ

The island of Okinawa belongs to the Ryūkyū archipelago at latitude 26° 19’ north and forms the southernmost of Japan's 47 prefectures. With a population of nearly 1,371,000, it has the highest rate of centenarians and the greatest health span in the world [13]. The unique Okinawa food traditions reveal cultural influences from both the Japanese mainland and ~~from~~ China; especially the latter contributed to the concept of food as a kind of medicine, a statement that in Western history is paralleled by the relevance of food in Hippocratic writings [14]. The Okinawa food culture has three main characteristics: (i) emphasis is placed on food mixtures rather than single foods, with particular attention to their combinations; (ii) mixed dishes encompass both plant and animal products (e.g. garlic and carrots and pork liver, or vegetables and freshwater fish); and (iii) the tendency to include locally available foods rather than those prescribed by the classical Chinese medicine handbooks [15]. The intelligent use of all edible parts of pork, including tail, paws, ears, internal organs, blood and fat is particularly remarkable; this tradition is quite different from that of mainland Japan [16, 17] where a plant-based diet has prevailed at least until the 18th century, probably due to the influence of Buddhism and Shintoism [18]. In Okinawa, the spread of pig raising had historically to await that of the sweet potato; this root tuber, native of Mexico, spread to Europe and Asia after the colonization of America. In Japan, it was introduced by the Portuguese in the 16th and 17th centuries [19] and quickly became crucial in preventing famines when harvests of rice were scarce [20]. The spread of the sweet potato, in turn, made intensive pig farming possible, and started a new era of “pork and sweet potato” culture that holds a prominent place in Okinawa food culture even today. The use of the pork’s cartilage and tendon parts increases the supply of collagen and elastin [15], important sources of the amino acids proline and hydroxyproline, which in turn play a crucial role in cell proliferation and differentiation, wound healing and polyamine synthesis [21]. The latter are precursors of epigenetic modulators [22] and are beneficial to cognitive performance [23]. Although pork’s whole fat was traditionally consumed in Okinawa, in modern cooking pork fat is carefully removed during a boiling procedure called *akunuki* (あくぬき) [17]. Although pork meat was traditionally salted for its preservation, the population of Okinawa is known today for having the lowest consumption of salt in Japan [24], which partly explains its lower mortality from cardiovascular disease and stroke.

In addition, the Okinawans' traditional consumption of seaweed varieties is ultimately attributable to cultural and historical influences [15]. Kombu seaweed (*Saccharina latissima*) contains large amounts of iodine, which is necessary for growth, and provides a good source of glutamic acid; it also contains dietary fibre and essential *n*-3 polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexaenoic acid [25]. Bitter gourd "Goya" (*Momordica charantia*) contains momordin which exerted a hypoglycaemic effect in an experimental rat model by activating peroxisome proliferator-activated receptors delta [26]. Herbal products derived from some plants uniquely grown in Okinawa possess an inhibiting effect of the kinase activity of PAK1 and therefore potentially enhance antioncogenic and anti-aging-promoting activities [27]. In addition, Okinawans regularly consume soybean-derived tofu, the high isoflavone content of which can have a healthy impact, depending on the amount consumed [28]. The relative deficiency of sulphur amino acids in soy protein is offset by the consumption of brown alga "ito-mozuku" (*Nemacystus decipiens*), also rich in fucoidan, which has various physiological and biological activities. However, in a recent study, the intake of vegetables and fruits was not significantly associated with a decreased risk of cardiovascular disease and stroke in Okinawa [29].

The exceptional longevity of the Okinawan population has also been reported to be related to a calorie-restricted diet [15, 30-32]. It is known that in experimental animals, a 30–60% reduced energy intake without malnutrition extends life span [33-36]. Since the life-prolonging effects of calorie restriction have been observed along the entire evolutionary scale from yeasts to non-human primates, it is also presumed to be applicable to humans. Some data seem to suggest that the average daily energy intake of the Okinawa population is lower than in mainland Japan; for instance, according to Suzuki, the calorie intake of Okinawan centenarians is as low as 1407 kcal/d (5.886 MJ) among men and 1096 kcal/d (4.586 MJ) among women [30], whereas according to a study by Willcox et al. the calorie intake among septuagenarians would be lower than 2000 kcal/d (8.368 MJ) [32]. Other estimates have provided higher values, for example in the Taishō period (from 1912 to 1926), the calorie intake would have been 2395, 2868 and 3650 kcal/d (10.021, 12.000 and 15.272 MJ), among teachers and public officials, part-time farmers and full-time farmers, respectively [15]. However, the cited research [15, 30-32] used different methods in assessing the energy intake, which may cause a potential bias. In any case, it is likely that the average energy intake of Okinawans has varied over time, and it is hardly credible that the new generations born after the Second World War still adhere to calorie restriction comparable to that of previous generations, or animal models. It is also worth mentioning that Okinawa's drinking water is rich in minerals, especially calcium, since the soil of Okinawa contains limestone originating

from the coral reef [37], and water rich in calcium and magnesium reduces cardiovascular mortality [38].

4. Ikaria BZ

Ikaria is a small Greek island located in the central-eastern Aegean Sea at the north latitude of 37° 35' and its population of nearly 8,000 enjoys a life expectancy comparable to that of the other long-lived populations already identified [8]. The longevity of Ikaria's inhabitants is mentioned even in historical documents. The Archbishop Joseph Georgirenes, who spent five years in Samos and Ikaria in the 17th century before going to Italy and finally to England, left a written report of the island; although he described the humble conditions of the islanders, he also mentioned their exceptionally good health and, remarkably, long life, which he generically attributed to the quality of the air and water [39].

The diet of Ikaria is a typical Mediterranean regimen, which is so far considered the only diet that demonstrably extends lifespan [40]. The degree of adherence to the Mediterranean model by the inhabitants is quite high [41] and is inversely correlated with comorbidity and metabolic dysfunction [42].

The Ikaria island is endowed by a biodiversity-rich ecosystem due to its geographical position at the crossroad of Europe, Asia and Africa [43], and the vast majority of its population adopts a plant-dominant diet rich in lettuce, green onions, chickpeas, lentils and fresh fruit. At least one third of residents eat local products exclusively, and the remainder buy them partly at the grocery store [44]. In the Ikaria BZ, the most commonly used fat is the locally produced olive oil which has a higher concentration of polyphenols, oleuropein and ligstrosides than oils popular on the other Aegean islands [45], and is consequently able to protect blood vessels from atherosclerosis [46]. At least 52% of the inhabitants of Ikaria consume a tea obtained from the infusion of the endemic plant *Sideritis sipylea* [47, 48]. Various in vitro studies have demonstrated an anti-inflammatory, antimicrobial and gastroprotective effect of the aqueous extract of *Sideritis*, which also affects the central nervous system as a modulator of GABA receptors [49]. Therefore, the Ikaria tea could possibly have a psychotherapeutic effect similar to serotonin and dopamine reuptake inhibitors and could relieve anxiety, depression and attention deficit disorders [50]. In addition, the MEDIS study evaluating the effects of long-term tea consumption showed that one to two cups a day were associated with a 70% reduction in diabetes mellitus regardless of age, sex, smoking and physical activity [51].

In the Ikaria BZ, the elderly population's consumption of coffee is traditionally very high: 87% of the inhabitants consume boiled Greek coffee and a linear relationship has been described between the consumption of coffee and the improvement of endothelial function [46]. Although coffee has been counted among the possible foods with beneficial effects on the Ikarians' health, the alleged properties of this beverage must be critically evaluated. Coffee contains brown pigments (melanoidins) with a strong antioxidant action. Some studies suggest that moderate coffee drinkers experience a mild reduction in cardiovascular risk [52], while others show that coffee extract can act in vitro as a pro-oxidant because the natural antioxidants in coffee are exhausted during roasting, although this loss is compensated by the generation of new antioxidant compounds which eventually prevail [53].

Despite living on an island, Ikarians do not eat large quantities of fish: [51]; instead, they consume a moderate amount of goat meat, milk and cheese, as is logical to expect in a mountain population dealing with livestock raising.

There is no evidence of any appreciable calorie restriction: the traditional fasting prescribed by the Greek Orthodox Church consisting of a vegetarian diet including exclusively of fish and seafood is not respected by 54.9% of the Ikaria residents [44], although a possible role of time-restricted feeding in Ikarian longevity still needs to be investigated.

5. Sardinia BZ

Sardinia, a Mediterranean island off the western coast of Italy, at latitude 40° 4' north, was historically characterized by its long-standing isolation and the peculiar genetic make-up of its inhabitants. Over the centuries, various peoples from the sea tried to invade and colonize it, but with the exception of Romans, they mostly remained in the coastal areas without penetrating inland [6]. The native population, a community of seminomadic shepherds who lived on livestock, was forced to retreat to the central mountainous area (*Ogliastra*) to maintain a relative independence and developed a unique culture and diet quite different from the rest of the population living in the lowlands [54]. Although the current diet of the Sardinia BZ can be considered a variant of the Mediterranean one and observes a relatively high consumption of animal foods such as cheese, meat and pork fat, it derived historically from a mixture of Roman agricultural traditions and pre-Roman pastoral habits rooted in the Bronze Age [55].

In the Sardinia BZ, sourdough wheat bread was the main staple food [54, 56]. A 2008 study showed that this food is able to lower postprandial glucose levels by 25% compared to the yeast-leavened

bread being consumed more recently [56]. The local minestrone (vegetable soup) containing onions, fennel, carrots and legumes (beans, broad beans, peas) as well as a large number of potatoes was also very common. However, the traditional minestrone was enriched with small chunks of salted fat bacon. The consumption of carbohydrate-based foods has been associated with the positive effects on life satisfaction of the Sardinia Blue Zoners [57].

Unlike in most Mediterranean areas, the diet of the Sardinia BZ was influenced by two crucial aspects: (i) the legacy of the pastoral culture based on cattle breeding which characterized the natives before the Roman rule; (ii) the effect of nutrition transition (NT) which started in the mid-1950s and expanded food choices over the second half of the past century, favouring a wider variety of foods. More specifically, before NT, the ratio between plant and animal food consumption was clearly biased in favour of the latter, especially for dairy food which was the major source of protein [58] and may have contributed to the preservation of muscle mass among the elderly, in line with the findings of the NHANES III study [59]. After 1950, following the improved economic conditions of the island, there was a progressive increase in the consumption of vegetables and fruit, which made the Sardinia BZ diet much more balanced and closer to the ideal Mediterranean model. Until recently the consumption of lard and fat bacon in Sardinia prevailed over that of olive oil [54]. However, the potential harmful effect of consuming a food rich in saturated fatty acids on the cardiovascular system was probably counterweighted by its high content in vitamin D, known to play a positive role on longevity [60], and choline, which promotes lipoprotein disposal from the liver and reduces the risk of fatty liver disease [61]. The Sardinia BZ diet is often praised for its high content in antioxidants; however, they are essentially limited to red wine and coffee, as the consumption of fresh fruit was traditionally low [54]. Corder et al., hypothesized that the consumption of red wine, rich in resveratrol and proanthocyanidins, may represent one factor responsible for the lower cardiovascular mortality of the Sardinia BZ population [62]. These phenolic compounds, present in local red wine extracts, could help countering age-related inflammation, as they decreased the release of inflammatory cytokines in an in vitro model of human Caco-2 enterocytes [63]. However, red wine's healthy effect is limited to light and moderate consumption, i.e., the typical drinking pattern of Mediterranean countries where it is taken regularly only during meals. When a certain threshold is exceeded, the deleterious effects of alcohol overtake its cardioprotective effects [64, 65]. Antioxidant properties have also been attributed to coffee, a drink widely used in the Sardinian BZ: our study reported that over 40% of participants consumed it at least three to five times a week, and about 25%, every day [54]. However, the effect of coffee on mortality is still a matter of debate [66].

The role of calorie restriction on Sardinian longevity has been hypothesized [67] although the historical data available, which indicate an average daily intake of 2400-2700 kcal/d (10.048-11.304 MJ) [58, 68, 69], seem to exclude an energy restriction comparable to that attained in experimental models. Rather than a reduction in the total amount of daily calories, this population could instead be characterized by a reduction in the number of hours dedicated to food intake [70], as time-restricted feeding protects against pathological conditions and promote healthy ageing [71].

6. Nicoya BZ

The Nicoya Peninsula is a north-western region of Costa Rica that juts out over the Pacific Ocean at the latitude of 10° 9’ N. It corresponds to the province of Guanacaste and hosts a population of approximately 161,000 inhabitants. The longevity of the Nicoya BZ population exhibits a male-biased lower mortality [72] and its food culture is historically derived from multiple influences such as: (i) the traditions of the pre-Columbian natives, the Chorotegas, who consumed corn-based foods [73]; (ii) the influence of the Aztecs who spread tamales, mixtures of meat, rice and vegetables mixed with corn flour, lard and spices, steamed in a plantain leaf; (iii) the European influence following the Spanish conquest of the country.

Various studies have analysed the diet of Nicoyans in relation to their large numbers of exceptional survivors [74-77]. In general, the diet is rich in plant-based foods, but the frequency of consumption of meat and dairy products is by no means negligible. However, rice and black beans are the staple of Nicoyan meals, and theirs association with lower cardiovascular mortality has been described [78]. Similar to other tropical countries, Nicoya’s diet is known for its high content of fruit such as mango and papaya. A 2017 study of Nicoyans aged between 90 and 109 years revealed that 74% of them ate fruit one to three times a day, and the remainder two to six times a week [75]. In addition, the consumption of tubers (potato, sweet pruned, cassava) varied from two times a week to three times a day in 88% of the participants. Notwithstanding, carbohydrate-based foods consumed by Nicoyans have a low glycaemic index [72], which may have delayed the onset of metabolic diseases. However, the consumption of animal protein-based products is also considerable in the Nicoya Peninsula: a study published in 2020 reported that 79% of centenarians consumed dairy products one to three times a day, and a further 12% at least twice a week [76]. This finding is in line with reports by Shimizu et al. about the increased survival of centenarians who prefer dairy to vegetables [79].

At least half of the oldest Nicoyans ate three to five servings of meat per week, and as much as 25% every day [76]. Interestingly, the most frequently consumed meat was pork, albeit in moderate quantities. An investigation on dietary patterns performed through principal component analysis revealed that the consumption of grains (white rice) in Nicoya was associated with a greater telomere length, a biological marker of longevity; this might be because rice, especially brown rice, is a proxy of the traditional diet in Nicoya [77]. Nicoya's diet does not seem to be characterized by calorie restriction as the CRELES study reported that the average energy intake of Nicoyans is significantly higher than that in the rest of the country [72]. However, the high calcium and magnesium content of Nicoya's drinking water could have lowered the cardiovascular mortality rate of the population [80, 81].

7. Comparing the BZs diets

Interest in the diets of long-lived populations stemmed initially from the hope of identifying specific foods or food patterns which could help to slow down the aging process and maintain a high functional level, even in old age. This possibility, not always supported by accurate scientific information, caught the media's interest, and fuelled a pervading subculture aimed to increase tourism and the trade of local products. From a critical viewpoint, this calls for a few considerations. First, the diets adopted in the various Blue Zones are quite different from each other, as may be expected when considering the different historical backgrounds, cultural traditions and environmental features of their populations [82] (Table 1). For instance, the prevalent consumption of self-produced foods, antioxidant-rich diets, moderate intake of pork meat and low consumption of fish likely result from the local availability of food resources. Second, the BZ communities were mostly isolated throughout their history, with limited market exchanges insufficient to ensure food variety. The pork-eating culture was shared by the Okinawa, Sardinia and Nicoya BZs, albeit with differences in meat preparation, preservation and frequency of consumption, whereas in the Ikaria BZ goat meat intake prevailed. Notably, meat consumption was always moderate in each BZ, and livestock was mostly raised in the wild graze on highly biodiverse soils, making the meat more nutritious and less harmful than that from intensive farming and large retailers. In addition, the moderate consumption of fish, recommended in the Mediterranean model, was not particularly frequent in the Ikaria and Sardinia BZ where shepherds outnumbered fishermen and dairy food provided adequate protein supply to maintain lean mass, especially for those in old age.

The impact of a calorie-restricted diet, initially hypothesized for all four BZs diets, was observed in the Okinawa BZ but not documented in the other long-lived communities [8]. The intense physical

activity commonly practiced by the other three BZ populations was hardly compatible with a low energy intake. However, food intake was limited to a short fraction of the day in these zones (i.e. time-restricted feeding) which has the same effect of an actual calorie-restricted diet [71].

One feature shared among the BZs is the relatively high consumption of legumes and potatoes [54]. Although in the literature a potato-rich diet is considered less healthy than most plant-based diets [83], this is mainly due to the cooking method (frying), and a recent article emphasizes that, in Sardinia, potatoes were consumed boiled and seasoned with fats capable of lowering its glycaemic index [84]. While it is universally recognized that the Mediterranean diet promotes health and possibly longevity as well [40], not all Mediterranean populations adopting it are equally long-lived. More importantly, the Ikaria and Sardinia BZs, the only ones located in the Mediterranean, show relevant deviations from the Mediterranean model that deserve to be further explored. It must be remembered that food preservation without refrigeration was ensured by salting (especially pork meat and few kinds of freshwater fish), and food transportation/distribution without an efficient road network was a chimera.

An additional aspect worth considering is that the diet of a community is rarely fixed but rather a model in progress where traditions comply with societal evolution. The BZ diets are not an exception, and they underwent the nutrition transition (NT) that resulted in marked differences between temporally distant generations. According to the conventional view proposed by Barry Popkin [85], the NT is a transformation that occurs in a given generation due to social and economic development, and it has a tendency to worsen the health properties of the original diet, although in some cases the opposite may have occurred [84]. If for some BZs, such as Okinawa, the NT determined the abandonment of traditional eating habits in favour of an imported Western diet, for others, such as the Sardinia BZ, it probably rebalanced some features of the traditional diet by introducing corrective measures (higher consumption of fruit and vegetables, fish, and lower consumption of salted meat, fat bacon and lard) which may have had a beneficial impact on health [84, 86]. Although in Ikaria the diet seems more stable over time, this could be a perspective error due to the lack of longitudinal data.

Finally, the diets should be considered in the broader setting of the population's lifestyle. Some negative aspects of a BZ diet, e.g., an excess of saturated fat, may have been partially counterweighted by an active lifestyle: this seems the case for the Sardinian BZ’s diet, as the intense daily physical activity, practiced by a pastoral community may have minimized the harmful effects of an excess of potato-derived starch and fat of animal origin [76, 84]. Even more important,

some peculiar genetic factors present in the BZ populations may have blunted the relative importance of the diet as a contributing factor in longevity.

8. Conclusion

While it can be concluded that our study of the dietary patterns of long-lived populations did not meet expectations, there is potential for future research focused on the specific reasons for the long lifespans of Blue Zone inhabitants. The evidence currently available does not allow for recommending the adoption of a diet that might be considered as being ‘BZ specific’ outside the context in which it was born and evolved over time, least of all on the pretext of promoting longevity. Some foods, —not all— frequently consumed in the BZs are safe and even beneficial to human health in general, while others have no significant effect or have potential adverse effects that have possibly been mitigated by the healthy lifestyle of the population as a whole. The Blue Zones appear to be fragile communities and it is not possible to predict whether they will continue to exist in the future, as in some of them there are early signs of a decline of their longevity advantage [87]. Despite the obvious challenges of adapting these diets to the general population, investigating the Blue Zones' eating regimes and their historical evolution makes for an exciting field of study.

Table 1. Basic characteristics of the four BZs.

	Okinawa BZ	**Ikaria BZ**	**Sardinia BZ**	**Nicoya BZ**
Population	1,285,000	8,300	56,000	161,000
Ethnic groups	Asian	White caucasians	White caucasians	Native Americans, White caucasians
Cultural influences on dietary practices	Neolithic Jōmonese, Chinese, Yamato Japanese	Greeks	Bronze Age settlers, Romans	Chorotegas, Aztecs, Spaniards
Traditional occupation	Agriculture	Animal husbandry	Animal husbandry	Forestry work
Climate	Subtropical[8]	Mediterranean[8]	Mediterranean[8]	Tropical[8]
Daily energy intake per capita (kcal)	< 2000[31]	<1500[88]	2,600[58]	2,392[89]
Obesity rate (%, BMI ≥ 30 kg/m²)	10–40[90]	12.5[88]	9.8[91]	23.6[76]
Frequency of intake in times/wks*				
Vegetable	5.0	4.1	2.3	6.1
Fruits	4.0	4.8	3.2	4.5
Total dairy	3.0	n.a.	6.4	3.6
Meat, poultry	1.0	1.5	1.5	3.2
Fish	0.5	1.8	0.4	1.3
Alcoholic beverages	++[92]	+[9]	++[9]	++[76]
Hardness in drinking water	++[37]	_[93]	+[94]	+++[80, 81]

*Authors' elaboration from different sources

Contributors

Giovanni Mario Pes contributed to drafting the article.

Maria Pina Dore contributed to drafting the article.

Giovanni Mario Pes, Maria Pina Dore and Michel Poulain contributed to conception and design of the work, drafting the article, data analysis and interpretation.

Michel Poulain and Fotini Tsofliou contributed to critical revision of the draft article.

All authors approved the final version and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare that they have no competing interests.

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