



Centenarians: A Narrative Review

Tiffany Field*

Departments of Pediatrics, Psychology, University of Miami/Miller School of Medicine and Fielding Graduate University, Florida, USA

ABSTRACT

Centenarians (100-109- years-old) were as many as 573,000 as of 2020. Most of the recent literature has been focused on identifying the unique characteristics of centenarians or predictor variables for their longevity. These have included genes, female gender, personality traits including extroversion and optimism, stress avoidance, resilience, social engagement, nutrition (especially Mediterranean or other Blue Zone diets), no smoking or chronic diseases, and physical biomarkers including low BMI, LDL and diastolic blood pressure. Although many negative effects have been expected for being centenarians, loneliness and frailty were the only prevalent problems in this recent literature. Although the lifestyle factors already mentioned have contributed to longevity, the most frequently discussed underlying mechanism has been chronic inflammatory status called “inflammaging” which has apparently been adaptive and less detrimental for centenarians than for younger aging samples. Unfortunately, studies on centenarians have been limited to cross-sectional or retrospective data, as the research on predicting extreme longevity has been relatively new.

Keywords: Social engagement; Cognition; Longevity

INTRODUCTION

This narrative review involved entering the term centenarians to find literature from the last five years on PubMed and PsycINFO. The search yielded 265 papers. However, following exclusion criteria including case reports and non-English papers, this review is a summary of the research reported in 34 papers. The recent literature on centenarians is predominantly focused on predictors of longevity or positive characteristics of being a centenarian. This narrative review is divided into sections on prevalence of centenarians, predictors/positive features, and expected negative effects. These are followed by sections on potential underlying mechanisms for longevity and methodological limitations of this recent literature. Among the contributory factors to the onset of cachexia we can list anorexia and metabolic alterations, i.e. increased inflammatory status, increased muscle proteolysis, impaired carbohydrate, protein and lipid metabolism. Inflammation does play a crucial role in its pathogenesis and its presence allows for cachexia identification.

Prevalence of centenarians

The first article on longevity as a human desire was published in 1838 when the average life expectancy was 40 years [1]. And, in 1842, although the average lifespan in Belgium was only 32 years, 16 centenarians were living there (the oldest being 111) [2].

The prevalence of centenarians (age 100-109) has increased from 417,000 in 2015 to 573,000 in 2020 (a 38% increase in just 5 years). And the prevalence is predicted to reach 19 million by the year 2100 [1]. As these authors have suggested, most children born in developed countries since the year 2000 will become centenarians. Reputedly, most centenarians will reach that age because they can postpone age-related pathologies (e. g. heart disease, stroke, COPD, cancer, respiratory infection, type 2 diabetes, osteoporosis and dementia). And they have several positive lifestyle activities like a nutritious diet and physical activity as well as positive attitudes including stress avoidance and resilience.

These large numbers of centenarians are surprising given that the average global life expectancy is 71 years, although significant variation has been noted across countries, e.g. Sierra Leone at 48 years, U.S. at 79 and Monaco at 87 [2]. Some places like the Blue Zones are home to many centenarians including Okinawa in Japan, the Nicoya peninsula in Costa Rica, Ikaria in Greece, Sardinia in Italy and Loma Linda in California [1]. The longevity of these centenarians has been attributed to a genetic predisposition, stress avoidance, resilience (an increased ability to respond to minor stressors of daily life) and a positive lifestyle in general with good nutrition in particular. The Blue Zones are said to have nine principles including strong family connections, close social engagements, meaningful life purpose, low intensity physical activity throughout

Correspondence to: Tiffany Field, Departments of Pediatrics, Psychology, University of Miami/Miller School of Medicine and Fielding Graduate University, Florida, USA; E-mail: tfield@med.miami.edu

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the day, staying stress-free, moderate alcohol consumption, belief in a higher power and especially good nutrition (high amounts of legumes, nuts and vegetables, avoiding over-eating and applying caloric restriction) [1].

Predictors or positive characteristics

Many predictors or positive characteristics have been noted for centenarians. These include genes, female gender, demographics, personality characteristics including extroversion and optimism, stress avoidance, resilience, social engagement, nutrition, no smoking, no chronic disease and biomarkers including lower Inflammation (Table 1).

Genes

Hundreds of genes have been implicated as influencing longevity (300–750 genes) [2]. These authors have given examples including oxidative stress genes (SOD3, HSPA) and a glucose metabolism gene (IGF-1) and they claim that heritability approximates 30 per cent, although other estimates have suggested 38 per cent. Phenotypic variation, as expected, has been partitioned into genetic and environmental variance components. Given that the research on genetic components of longevity is larger and more complex than the 750 genes reported, this literature review does not include a discussion of genetics, except to acknowledge their importance.

Demographics

Some demographic variables were addressed in a study from China. In what the authors labeled “the largest sample of centenarians in the world”, centenarians (100-109 years-old) were compared with nonagenarians (90-99 years), octogenarians (80-89) and younger elders (65–79) from the Chinese Longitudinal Health Study which involved face-to-face interviews (N=12,047 centenarians) [3]. Eighty-eight per cent of the males were widowed and 98% of the females. The majority of the centenarians lived with family members. Fewer of the rural centenarians were satisfied with life compared to urban centenarians (62% vs. 69%). But, a greater per cent of the rural centenarians were performing better on activities of daily living (54 vs 37%). The authors suggested that this finding was related to the centenarians living in a more natural environment that was healthier and that they continued gardening. The gardening and the natural environment variables were, of course, confounded in this study.

Gender differences

Gender differences in centenarians have frequently been reported, typically suggesting that female centenarians live longer. In the longevity study from China already mentioned, women lived

longer but experienced worse health [3]. A greater number of males had better health (56 vs. 51%), had more active activities of daily living (51 vs. 46%), better cognitive function (43 vs. 25%) and less disease (39 vs. 46%). However, significant gender disparity was noted for several confounding variables including males having greater socioeconomic status, education and outdoor activity and less disease.

Other gender differences that might affect longevity were noted in a study from Belgium (N=3000) [4]. In that sample, male centenarian lived two times longer with spouses than female centenarians. Females lived alone for more than half their lives. Males also had younger spouses and females had older spouses. Most of the centenarians from the sample ended their lives in a nursing home, but very late in life.

In a study entitled “Centenarians born before 1919 are resistant to COVID-19”, the oldest females in the Sicilian sample were the most resistant (Caruso, et al.). The authors related that finding to the women’s exposure to the 1918 Spanish flu epidemic, giving them antibodies.

Most of the super centenarians (110-122 years-old) are also females [5]. These authors noted that this sex gap in longevity is also common in non-human animals, especially mammals. They related this to the “cost of sexual selection and sexual dimorphism”. They further elaborated this mechanism as mitochondria being transmitted through females in most species, a phenomenon that has been labeled “the mother’s curse”. They noted that in Calabria (southern Italy) there have been twice as many female centenarians. The sex gap has also been noted there in super centenarians with the oldest female being 122 years-old (a longevity record). Another theory they advanced is that estrogen with its antioxidant and anti-inflammatory properties, in contrast to testosterone, is protective against many diseases.

Personality characteristics

Personality characteristics have also been the focus of research on centenarians. In one study, 65% of centenarians were noted to be extroverted, 50% open-minded and 35% emotionally stable [6]. The authors suggested that these personality characteristics contributed to more than 50% of the sample being free of depression and anxiety.

In the Chinese longevity sample, centenarians were noted to be more resilient than other age groups [3]. Resilience was defined as the ability to adapt positively to adversity including having personal tenacity, optimism, secure relationships and self-control and coping with negative mood. Nonagenarians (90–99 years-old) who had psychological resilience had a 43% greater likelihood of becoming centenarians.

In a study entitled “Storytelling reveals the active, positive lives of centenarians”, 16 healthy centenarians from the UK were living as independently as possible and continuing their growth and development and their ongoing close relationships [7]. Their stories revealed a positive picture of aging, thus counteracting negative stereotypes. When asked about difficulties and loss, their expressions were “accept whatever life brings”, “just plod on”, and “do what you can to make things better and then move on”.

Social engagement

Although social engagement or social connection is one of the nine principles of the Blue Zones, only one study on social connection could be found in this recent literature on centenarians. In

Table 1: Predictors/positive characteristics of centenarians.

Predictor	First author
Genes	Eovirdaraju
Demographics	Zheng
Gender differences	Zeng, Poulain, Caruso, Marais
Personality characteristics	Tafaro, Zeng, Koch
Social engagement	Hso
Nutrition	Dacic, Dominguez, Crous-Bou, Gu
Chronic diseases	Barak, Ioakeim-Skoufa
Biomarkers	Hai, Zeng, Dacic

this study from Taipei, typologies of loneliness, social connection and living alone were formed to determine their relationships with psychological well-being [8]. The largest group was the not lonely, socially connected and living with others (53%). The not lonely, not socially connected and living with others comprised a smaller percent of the sample (27%). And very small numbers were noted for the lonely and socially connected (5%) and the lonely, not socially connected but living with others (7%). As might be expected, the lonely groups were more depressed and had less life satisfaction, but the lonely only comprised 12% of the sample and only 5% lived alone, so the living arrangement was not the determinant of loneliness or the lack of social connection. Although loneliness has been a negative effect of being centenarian in several studies, it was infrequent, at least in this sample.

Nutrition

The Blue Zone diets have been described in a couple recent reviews of the literature. In one of the reviews, the Okinawa diet was described as being calorie restricted starting at an early age in young children and continuing years later among septuagenarians [1]. The diet of Sardinia in this review was described as a plant-based diet with high cereal intake and some poultry. The centenarians of Ikaria were noted to follow the Mediterranean diet. However, other variables like family solidarity, social interaction and physical activity have, not surprisingly, confounded the nutritional effects in these Blue Zones.

In the second review, the Okinawa diet was described as being 80% calories from veggies, small amounts of fish and limited lean meat, and sweet potatoes was the main source of carbohydrates [9]. The Japanese diet was described as being rice, veggies, fish, soy, green tea and seaweed and 80% less fat than the Mediterranean diet. These authors described Japan as having “the longest life expectancy and having the greatest number of centenarians”. The Nordic diet includes fish, cabbage, root veggies, berries, potatoes, rapeseed oil and fish (salmon, sardines, mackerel and herring). The Mediterranean diet was said to have the largest number of publications and was plant-based including colorful veggies, fruit, nuts, grains, olive oil, fish, dairy products, eggs and wine and only occasional animal-derived food. The Loma Linda, California diet was suggested to be the only fish-vegetarian (pescatarian) diet with the centenarians residing there reputedly having the “lowest incidence of mortality”. However, as many as 9000 of those living in Loma Linda belong to the Seventh Day Adventists, which has potentially confounded the effects of their diet.

The authors of this review suggested that fruits and veggies have been inversely associated with non-communicable diseases because of their antioxidant and their anti-inflammatory properties [9]. In addition, they increase energy, fiber, satiety, glycemic control, blood lipids and gastrointestinal function. They are also sources of phytochemicals such as polyphenols, carotenoids and phytosterols.

In a paper entitled “Plant-rich dietary patterns, plant foods and nutrients and telomere length”, telomere length was shortened by inflammation and oxidative stress [10]. But plants as antioxidants as well as anti-inflammatories slowed this process. The authors suggested that centenarians were following a Mediterranean diet for that purpose, i.e. consuming seeds (nuts, grains and coffee) and colorful veggies (providing carotenoids).

In a study from Canada that highlighted the importance of diet, centenarians (N=122) were compared to aging adults 65-86-years-

old (N= 12,626) [11]. The frequency of food consumption was measured over the last 12 months. The aging adult group had a western diet (french fries, red meat, processed meat) more frequently than nutrient rich vegetables, fruit, nuts and whole grains. The aging adults also used alcohol more frequently. The authors attributed these findings to the aging not only having a poor diet but also being less educated and more frequently living alone. They suggested that the aging adults may have been more fatalistic as they “approached the end of their lives”. Further, they mentioned that the national dietary guidelines were not modified until the 1980s in Canada. Physical activity was not measured in this study and methodological problems included the two groups being from different generations and having unequal sample sizes, thus limiting the reliability of the findings.

Chronic diseases

Centenarians have also reputedly been free of chronic diseases as compared to older adults. This has been demonstrated in a few studies. In a paper entitled “The great escape: Centenarians exceptional health”, centenarians (N=292) were compared with elderly adults (N= 103,377) from New Zealand [12]. As would be expected, there were more women in the sample (75%). The centenarians were not only free of chronic diseases compared to the older adults but they were not smoking and there was a greater rate of social engagement in their group. In still another study, centenarians were compared to octogenarians and nonagenarians [13]. Centenarians had less prevalent chronic disease, drugs and polypharmacy. Once again the unequal sample sizes limited the power of these analyses resulting in lower reliability of these findings.

The Seven Countries Study that included prospective observations and trials on diverse samples attributed the absence of chronic non-communicable diseases to the Mediterranean diet that was being followed [14]. The Mediterranean diet was thought to be responsible for the prevention and management of age-associated, non-communicable diseases including cardiovascular, metabolic, neurodegenerative and respiratory diseases as well as cancer, depression, and fragility fractures. Other variables were not reported for this seven countries study.

Biomarkers

Biomarkers of centenarians have been highlighted in a few studies in this recent literature. In a paper entitled “BMI, blood pressure and plasma lipids among centenarians and their offspring”, centenarians (N=253) were compared with their offspring (N=217, mean age=70) [15]. The centenarians had a lower BMI (body mass index), lower LDL (low density lipoprotein) and lower diastolic blood pressure but higher systolic blood pressure. They also had less previous obesity but more previous hypertension. In a much larger sample (N=12,047), lower diastolic blood pressure was also reported [3]. In this sample, lower triglycerides were also noted as well as greater HDL (high density lipoprotein). In a review on the Blue Zone diets, the biomarkers that were noted included lower LDL, diastolic and systolic blood pressure [1]. These lower biomarkers likely relate to calorie restriction and nutritious diets reported for centenarians in these studies/reviews, although they may also be heritability factors.

Expected risk factors

Some risk factors have been noted for centenarians, but several

of the expected risk factors based on the aging adult literature have not been problematic for centenarians. For example, loneliness and frailty have been reported for centenarians by several investigators. But some of the problems that have occurred for those in their 70s, 80s and 90s such as feeling useless, having depressive symptoms, cognitive impairment and multi-morbidity have not been prevalent in centenarians. Most of these problems have been studied as individual predictors, although they could also be confounding factors.

Loneliness

As has already been mentioned, loneliness has been studied along with isolation in the context of living alone or with others [8]. In that study from Taipei on different combinations of loneliness, being connected and living with others, only the lonely groups were experiencing less life satisfaction and more depression. And, surprisingly, only 15% of that centenarian sample were experiencing loneliness.

In contrast, as many as 50% were experiencing loneliness in another study [16]. In this sample (N= 94), 30% were classified as isolated and lonely, 21% were lonely but not isolated and 29% were neither isolated nor lonely. In a sample from the Canadian Longitudinal Study of Aging (N=30,079), the socially isolated and lonely were more psychologically distressed, but the “only lonely” individuals were more distressed than the “only socially isolated” [17]. In a comparison of psychosocial variables associated with loneliness in centenarians *vs.* elderly individuals in New Zealand (N=191 centenarians with mean age of 101 and 73,095 elderly with mean age of 81), centenarians were more often female and widowed (89 *vs.* 43%). However, the prevalence of loneliness in centenarians was 32% less frequent and the prevalence of depression was 22% less frequent than was noted in the significantly larger sample of the elderly averaging 81 years [18]. Loneliness was more often associated with living alone and being depressed. The significant difference in the sample sizes, again, limits the reliability of these data.

In a review entitled “Social isolation and loneliness: the new geriatric giants”, social isolation and loneliness were surprisingly more associated with morbidity and mortality than smoking, alcohol, obesity and frailty in centenarians [19]. Several effective interventions were suggested including social facilitation (including technology), exercise, psychological therapies, health and social services, animal therapy, befriending, leisure and skill development.

Perceived uselessness

Perceived uselessness is another psychological variable that has positively differentiated centenarians from non-centenarians. For example, in a paper entitled “A comparison of perceived uselessness in centenarians and non-centenarians in China” (N=5778 centenarians and 20,846 non-centenarians), centenarians had a 31% lower risk of experiencing perceived uselessness [20]. Perceived uselessness was also 36-39% less prevalent in the centenarians than those who died at 91-94 years of age. Having purpose in life, as one of the nine Blue Zone principles, was apparently a protective factor for longevity in this sample.

Depression and anxiety

The prevalence of depression and anxiety has been low in the centenarian samples. And, typically, it has been studied in the context of activities that diminish depression and anxiety. For example, in a sample from China (N=288), 13% were expressing depressive

symptoms and 9% anxiety [21]. Diet diversity was negatively correlated with depression but not with anxiety. Directionality, of course, cannot be determined in this cross-sectional study. In another sample from China (N=1547), a greater prevalence of depression was noted at 20% [22]. However, this sample ranged in age from 80 to 116, so it included octogenarians and nonagenarians who were notably more depressed. And lower levels of red blood cells and hemoglobin were also noted in this multi-age sample, potentially confounding the findings.

In a paper entitled “Is the Sardinian blue zone the new Shangri-la for mental health? Significant associations were noted between depression symptoms, physical health and time spent gardening (N=318) [23]. Seventeen percent of the variance in the CES-D depression scores was predicted by perceived physical health and gardening, suggesting that those who engaged in gardening and had better physical health were less depressed or vice versa.

In another study, high religiosity and spirituality were negatively associated with anxiety and depression and positively associated with life satisfaction, meaning in life, social relations and psychological well-being [24]. This review on 102 studies (N=79,918) also showed that centenarians had less fear of death which may have related to their greater religiosity and spirituality.

Frailty

Frailty has been one of the negative effects of being a centenarian. It is typically based on the Fried Frailty Phenotype including at least three clinical signs of exhaustion, weight loss, weakness, slowness and low physical activity level [25]. In this study the Fried Frailty Phenotype was used and the most prevalent sign in this sample (N=1991, mean age =101) was weakness. Six percent of the sample was robust, 43% were pre-frail and 52% were frail. The Geriatric Depression Scale was also administered. And, based on the scores from that measure, 35% of the sample was depressed and of this group, 51% were frail, 21% were pre-frail and 0% was robust.

In a study on frailty and associated factors among Chinese centenarians (N = 1043), a logistic regression was conducted to determine risk factors for frailty [26]. In the logistic regression, the factors that predicted frailty were having less than 23 teeth with dentures, living alone or in an institution, lacking exercise, having insufficient financial resources and being female (Table 2).

Multi-morbidity

In a 13-year longitudinal study, Swedish centenarians (N=222) were compared with folks less than 100 (N=3573) [27]. When the centenarians were less than 85 they had slower health changes. After age 85 there was an acceleration of those problems. Four to nine years later, the sample of centenarians had multi-morbidity, disability and cognitive impairment. However, at 100 years, 39% of the sample was cognitively intact and 55% had escaped disability,

Table 2: Risk factors/negative effects of longevity for centenarians.

Negative effects	First author
Loneliness	Hso, Zaccaria, Menec, Leitch, Freedman
Perceived uselessness	Zhao
Depression and anxiety	Li, Sun, Ruiiu, Cielho-junior
Frailty	Ribiero, Zhang
Multimorbidity	Vettano, Croize-Pourvelot, Liu

but only 5% were free of multi-morbidity. At that time, the centenarians *vs.* the less than 85-year-old adults had more years of multi morbidity (nine *vs.* seven years), disability (four *vs.* three years) and cognitive impairment (six *vs.* four years).

Geriatric syndrome has been the label applied for multiple problems that have led to dependency for activities of daily living in centenarians [28]. In this sample of centenarians (N=23, 77% women), 59% were living in nursing homes and 79% were using walkers. Living in a nursing home was associated with greater cognitive impairment, more comorbidity and fewer hospitalizations. Given that the sample was self-selected as needing a nursing home, the medical staff at the nursing home would make it less likely for the residents to need hospitalization.

Metabolic syndrome is another physical problem that has affected centenarians [29]. In this sample (N= 2493), low levels of vitamin D were noted to lead to metabolic syndrome. Of this sample, 36% had insufficient levels of vitamin D and 41% were considered vitamin D deficient.

Potential underlying mechanisms for longevity

The most frequently proposed potential underlying mechanisms for the longevity of centenarians include inflammation, immune function and exposure to previous epidemics. In a paper entitled “A comprehensive analysis of cytokines network in centenarians”, 62 cytokines were studied [30]. An increase was noted in TNF- α and IL-6 as well as other pro-inflammatory cytokines like IL-23. No increase was reported for anti-inflammatories with the exception of Th-2 shifting (from more negative immune function) and an increase in the cytokine IL-19. Several growth factors noted to regulate immunity such as G-CSF were also up-regulated.

Some inconsistent data were reported in a recent review suggesting a decrease in TNF- α levels as well as C-reactive protein (both pro-inflammatory cytokines) [1]. These authors suggested that decreased circulating insulin and fasting glucose along with decreased energy expenditure and body temperature were also contributing to longevity.

The chronic inflammatory state called “inflammaging” has been reputedly adaptive and less detrimental for centenarians than for younger people, according to a review of several recent studies [31]. The same authors suggested that centenarians had longevity by being creatures of habit and eating meals at the same time of day which has facilitated circadian rhythms including stable sleep cycles.

In a study entitled “Immunosenescence in aging between immune cells depletion and cytokines up-regulation”, the markers of inflammation and adaptive immunity in centenarians are characterized by a decrease in CD⁺ cells and an increase in CD4⁺ cells [32].

This has also been reported by another research group suggesting that healthy aging was associated with a high CD4/CD8 ratio and a low production of pro-inflammatory cytokines [33]. In still another study on immunity and longevity, some drugs (riparmycin, metformin, selegiline) and antioxidants (vitamin C and E) have been noted to improve immunity and prolong the life span, as in a “remodeling of the immune system” [34].

Exposure to epidemics has also been noted in the history of centenarians. As has already been noted, the greater longevity of

females in Sicily has been ascribed to their exposure to the 1918 Spanish flu epidemic [35]. But it's not clear why the men were not also “immunized” by that epidemic. And the extreme longevity seen in the Sardinian blue zone has been attributed to exposure to malaria and shepherds' disease [36]. Even the survival of COVID-19 by women and older centenarians who were born before 1919 has been attributed to the 1918 Spanish flu [37].

Methodological limitations

Several methodological limitations can be noted about these recent studies on centenarians. Significant variability has been reported on the sampling methods, on the sample sizes, and the prevalence and results of the studies. The sample sizes for the centenarians were not surprisingly very small as compared to the less old groups, making the power of the analyses low and the results less reliable. Most of the methods have been self-report surveys. And, most of the data are from records or reports by relatives rather than the centenarians themselves.

The key variables, as often happens, have been “pet variables” or those favored by the authors. And, the data have been frequently analyzed *via* logistic regression analysis which controls for confounding variables that might have instead been risk factors or mediating/moderating variables if they had been analyzed by mediation/moderation or structural equations analysis. An example is that several researchers controlled for gender even though the prevalence data suggest that females have greater longevity perhaps because of estrogen levels. The findings that women were the more prevalent centenarians were not surprising, although their lesser health during their longevity was disconcerting. And does that suggest that estrogen may be less protective of health while its more predictive of longevity?

More studies have reported positive effects *vs.* data on negative effects. Several of the effects that have been noted could also be bidirectional, reciprocal variables, as in frailty and depression. Several of the scales are short or simply dichotomous which limits the reliability of those measures. Directionality cannot be determined as most of the studies were based on correlational data that have been collected retrospectively, as might be expected for centenarians as they are unknown until they reach 100.

Although many positive effects have been reported for centenarians as in very low prevalence of disease and depression, several studies highlighted the loneliness associated with longevity. The measures of loneliness and its effects are sufficiently variable that reviews have been inconclusive and meta-analyses have not been conducted. Loneliness would be expected to contribute to depression, so the low prevalence of depression was surprising. Despite these methodological limitations, the recent literature highlights the relationships between loneliness and longevity, although it doesn't conclude that aging is associated with more loneliness necessarily than at other stages of life.

The potential underlying mechanism studies have focused primarily on inflammation and immune function as being less problematic for centenarians than the very old (younger than centenarians). It is not clear why inflammation would be a significant problem for folks in their 80s and 90s but not in their 100s unless the younger adults had pre-existing conditions or less heritability of longevity. And the data suggesting that exposure to previous diseases like Spanish flu and malaria was protective highlights the importance of following those who have been exposed to recent

diseases like COVID-19. Nutritious diet and physical activity were the most prevalent positive lifestyle characteristics of the centenarians. The most compelling data may come from the five blue zones, although they are largely anecdotal and focused primarily on diet. And only small variations exist in those diets but enough variation that the variance in longevity that is explained by those variations is not known.

Despite these methodological limitations, the recent research on centenarians and the origins of their longevity is informative. At this time the importance of future research on centenarians is highlighted by their expected increasing prevalence. Super-centenarians are also being recognized in various parts of the world. And, the spread of the lifestyles of blue zone centenarians will contribute to growing numbers of centenarians and super-centenarians.

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