

1-1-2023

Old, Nonagenarians, and Centenarians in Cilento, Italy and the Association of Lifespan with the Level of Some Physicochemical Elements in Tap Drinking Water.

Silvana Mirella Aliberti

Richard H W Funk

Elena Ciaglia

Joseph S. Gonnella

Aldo Giudice

See next page for additional authors

Follow this and additional works at: <https://jdc.jefferson.edu/medfp>

 Part of the [Medical Education Commons](#)

[Let us know how access to this document benefits you](#)




This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Medicine Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Authors

Silvana Mirella Aliberti, Richard H W Funk, Elena Ciaglia, Joseph S. Gonnella, Aldo Giudice, Carmine Vecchione, Annibale Alessandro Puca, and Mario Capunzo

Article

Old, Nonagenarians, and Centenarians in Cilento, Italy and the Association of Lifespan with the Level of Some Physicochemical Elements in Tap Drinking Water

Silvana Mirella Aliberti ^{1,*} , Richard H. W. Funk ², Elena Ciaglia ¹ , Joseph Gonnella ³, Aldo Giudice ⁴, Carmine Vecchione ^{1,5}, Annibale Alessandro Puca ^{1,6}  and Mario Capunzo ^{1,7}

- ¹ Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana”, University of Salerno, 84081 Salerno, Italy
 - ² Medical Faculty Carl Gustav Carus, Institute of Anatomy, University of Technology (TU) Dresden, 01307 Dresden, Germany
 - ³ Center for Medical Research in Medical Education and Health Care, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA
 - ⁴ Epidemiology Unit, Istituto Nazionale Tumori IRCCS, “Fondazione G. Pascale”, 80131 Naples, Italy
 - ⁵ Vascular Physiopathology Unit, Department of Angio-Cardio-Neurology, IRCCS Neuromed, 86077 Pozzilli, Italy
 - ⁶ Cardiovascular Research Unit, IRCCS MultiMedica, 20138 Milan, Italy
 - ⁷ Complex Operational Unit Health Hygiene, University Hospital “San Giovanni di Dio e Ruggi d’Aragona”, 84131 Salerno, Italy
- * Correspondence: sialiberti@unisa.it; Tel.: +39-089-965227



Citation: Aliberti, S.M.; Funk, R.H.W.; Ciaglia, E.; Gonnella, J.; Giudice, A.; Vecchione, C.; Puca, A.A.; Capunzo, M. Old, Nonagenarians, and Centenarians in Cilento, Italy and the Association of Lifespan with the Level of Some Physicochemical Elements in Tap Drinking Water. *Nutrients* **2023**, *15*, 218. <https://doi.org/10.3390/nu15010218>

Academic Editor: Sonya Vasto

Received: 28 November 2022

Revised: 26 December 2022

Accepted: 29 December 2022

Published: 1 January 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Longevity, as a complex life-history trait, shares an ontogenetic relationship with other quantitative traits, such as epigenetic and environmental factors. Therefore, it is important to identify environmental factors that may modify the epigenome to establish healthy aging. This study explored the association between tap drinking water and longevity in Cilento, Italy, to understand whether trace elements in local drinking water may have an influence on old, nonagenarian, and centenarian people and promote their health and longevity. Data on population and water sources were collected through the National Demographic Statistics, the Cilento Municipal Archives, and the Cilento Integrated Water Service. Ordinary least squares (OLS) regression and a geographically weight regression (GWR) model were used to study the spatial relationship between the explanatory and outcome variables of longevity. The results of the study showed that the prevalence of longevity is concentrated in the central, northern and southeastern areas of the territory and that some trace elements present in tap water may contribute to local longevity in Cilento. Specifically, all Cilento municipalities had alkaline tap water, and the municipalities with the highest longevity concentrations had higher alkalinity levels than the other municipalities, soft to medium-hard water hardness, an amount of total dissolved solids equivalent to the level of excellent water, lower amounts of sodium, adequate iron concentration, and adequate dietary intake of manganese per day.

Keywords: longevity; old population; centenarians; physicochemical elements; tap drinking water; healthy living; Cilento region

1. Introduction

There has long been a global desire to be able to achieve greater longevity, not only in terms of overall lifespan, but especially regarding the possibility of increasing the healthy part of the life. To activate the strategies necessary to achieve this goal, a whole range of factors and the complex interactions among them must be considered. Many studies have shown that longevity is closely linked to genetic factors [1–4] and macro-environmental (climate, land, water) [5,6] and micro-environmental (lifestyle, social and community networks, socio-economic conditions) [7–9] factors.

Epigenetics (a term coined in 1942 by Waddington) studies the interconnected concatenations of factors that take place in the space between the genotype and phenotype. Environmental factors can trigger a series of changes in physiological developmental patterns through a process termed developmental plasticity, causing an individual to produce alternative phenotypes throughout life, and these changes can have beneficial effects on health [10].

In recent years, among the macro-environmental factors, special attention has been paid to the relationship between drinking water and physical health [11]. Water is essential to life [12]. On the other hand, in the human body, water is linked to almost all interfaces between internal structures, including ions, proteins, membranes, and organelles, and, due to its special physicochemical properties, many vital functions can take place regularly and create benefits [13]. Drinking water helps eliminate toxins and waste substances, normalizes body temperature, detoxifies and purifies the body, facilitates the transport of nutrients to cells, aids in digestion, and combats fatigue and tiredness [14]. According to the World Health Organization (WHO) [15], drinking water contains beneficial elements such as fluoride (F), iron (Fe), manganese (Mn), nickel (Ni), zinc (Zn), etc., which are essential for the growth of the human body and living organisms. Essential mineral elements are significantly assimilated through drinking water [15,16] and, depending on its physicochemical quality, may have a beneficial influence on, or cause risks to, health.

Several studies have examined potential human health risks from As, F and heavy metals in low-quality groundwater [17–19]. Some research has considered sodium content in water deleterious because it potentially induces hypertension, although chloride concentration may also contribute to this [20–22]. According to a study conducted in 76 municipalities in central Sweden on regional differences in cardiovascular disease mortality, a significant gradient was found between western areas with high mortality and soft water and eastern areas with low mortality and hard water [23]. Dore et al. [24] confirm the beneficial role of water high in calcium and bicarbonate against coronary heart disease. Other studies in animal models have shown positive effects on improved body weight and offspring development [25,26] with the use of alkaline water. In addition, several biological effects have been documented, such as antidiabetic and antioxidant actions [27], DNA-protective effects [28], and growth-promoting activities [26]. According to Sengupta [12] hard water is considered an important etiological factor, causing many diseases such as cardiovascular problems, diabetes, reproductive failure, neuronal diseases, etc.

The relationship between the characteristics of major drinking water elements in some typical longevity areas has been demonstrated by a number of studies [29–31].

In agreement with Hao et al. [29], a positive correlation was found between daily intake of copper (Cu), selenium (Se) and zinc (Zn) from food and water and indices of aging and longevity, and a negative correlation between lead (Pb) and indices of longevity. Liu et al. [32] found that moderate water hardness and higher strontium concentration in drinking water characterize municipalities with longevity compared with those with non-longevity. Research by Moretti et al. [33] using a short-lived invertebrate model (i.e., fruit flies) showed that the consumption of very low dietary doses of nitrite can increase the lifespan. However, the results were only evident in females, suggesting a possible sex-specific effect of this anion. The research results of Carvalho et al. [34] suggest that long-term consumption of inorganic nitrate is safe, does not increase the risk of death and does not affect the lifespan of animals, regardless of gender.

Therefore, the quality of drinking water from different natural environments could have a direct impact on local human health and longevity [15,31,32].

Despite numerous studies on the topic of longevity and correlations with various environmental factors, to the best of our knowledge, no research conducted in Cilento or other Italian regions has investigated the possible relationship between longevity and trace elements in drinking water at the municipal level. Therefore, we hypothesized that some physicochemical properties of drinking water may be protective factors for longevity.

The purpose of this study was to explore the association between tap drinking water and longevity in Cilento and to understand whether trace elements in drinking water can have a direct influence on local health and longevity and improve the living standards of the old, nonagenarians and centenarians.

2. Materials and Methods

2.1. Description of the Study Area: The Cilento Region

Geographically, Cilento is a subregion of the Campania region of southern Italy, in the territory of the province of Salerno, and has been declared a UNESCO World Heritage Site. The territory of Cilento covers an area of about 490,000 hectares and includes 102 municipalities. From the environmental point of view, it is a heterogeneous territory, characterized by the integration of different landscape types, including coastal, hilly and mountainous areas [5] and mouths of important waterways, and the morphological and climatic variability creates a potential not easily found in other areas of the Italian peninsula [35]. The geological nature of the rocks that make up the Cilento is twofold: the “Cilento flysch” (dense stratification of rocks) toward the northwestern coast, and the “limestone rocks” (generators of karst phenomena) that make up the inland (Alburno-Cervati) and southern mountain complexes of the Cilento and Vallo di Diano National Park [35]. Karst phenomena are one of the determinants of the lithological characteristics of Cilento waters [35,36], along with soil leaching and atmospheric precipitation [32]. It should be noted that Cilento has a large number of springs, scattered among the hills and near the coast [35,37]. In this area, man has been able to harmoniously integrate with the forms of landscape [38], in a rural, agricultural and pastoral civilization [5].

Cilento has a population of about 278,093 and maintains relatively high proportions of long-lived people (old, nonagenarians and centenarians), with a ratio of 40.31/1000 inhabitants [39]. The prevalence of centenarians remains at around the 12.49 ratio. With a substantial old population base, Cilento is an ideal region to examine whether regional longevity is associated with the properties of water elements.

2.2. Data Collection on Population and Water Sources

Demographic data were collected through the Cilento Municipal Archives in the years 2021–2022 and compared with ISTAT demographic statistics [5]. Longevity indicators were calculated from the collected demographic data and used as dependent variables in the study. Four longevity indicators were used in the research to reflect regional longevity [5], including the 85+ ratio (85+/total population) [40], the 90+ ratio (90+/total population) [40], and the Centenarian ratio (95+/55–64) [41,42]. To reduce the effect of important phenomena, such as declining birth rates and observed migration in regional territories, the Centenarity index (CI%), given by the ratio of centenarians to those aged 90 [43], was used (Table 1).

Table 1. Descriptive characteristics of longevity indicators among the 102 Cilento municipalities.

Indicators	Number of Municipalities	Min	Max	Mean	SD	Moran's I Index	Z-Score	p Value
85+ ratio	102	1	13.1	5.6	2.2	0.37	6.18	<0.001 **
90+ ratio	102	0.2	5.8	2.1	1.04	0.30	5.04	<0.001 **
Centenarian ratio	102	0	12.6	3.08	2.01	0.04	0.93	0.34
Centenarity index	102	0	10	1.9	2.6	−0.03	−0.33	0.73

Note: Min—minimum; Max—maximum; SD—standard deviation; ** denotes $p > 0.01$, indicates the statistical significance of the Moran's test; z-score indicate statistical significance of clustering (it must be greater than 2.58 at $p < 0.01$; p value probability of error in rejecting the null hypothesis).

Physicochemical parameters of tap drinking water from the 102 municipalities in Cilento, used in the research as independent variables, were collected through CONSAC Gestioni Idriche [37] and ASIS Salernitana [44], which provide integrated water services in the Cilento area. Parameter selection was based on review of the relevant literature and

availability of collected data and included: (1) hydrogen ion concentration (pH), where 7 indicates a neutral solution, a range from 0 to 7 indicates an acidic solution, and a range from 7 to 14 highlights an alkaline/basic solution [45–47]; (2) total hardness (TH), given by the concentration of calcium ions (Ca^{2+}) and magnesium ions (Mg^{2+}) [32], whose levels are as follows: 0–7 °F very soft water, 7–15 °F soft water, 15–22 °F medium-hard water, 22–35 °F hard water, >35 °F very hard water [15,45–47]; total dissolved solids (TDS), divided into the following levels: 50–150 excellent for drinking, 150–250 good, 250–300 fair, 300–500 poor [15]; and cations and anions, including sodium (Na^+), nitrate (NO_3^-), sulfate (SO_4), chloride (Cl), iron (Fe^{2+}), manganese (Mn^{2+}), and nickel (Ni) (Table 2) [15,45–47].

Table 2. Descriptive statistics of the level of element concentration in tap water in Cilento and Global Moran's I values.

Indicators	Number of Municipalities	Min	Max	Mean	SD	NS	WHO GV	Moran's I Index	Z-Score	p Value
pH	102	7.4	8.3	7.9	0.2	6.5–9.5	6.5–8.5	0.16	2.85	0.004 *
TH	102	9.6	34.8	19.7	4.8	15–50	15–50	−0.07	−1.34	0.17
TDS	102	110	370	219.6	58.1	1000	1000	0.21	3.57	0.003*
Na^+	102	2	19	5.2	2.7	200	200	0.02	0.61	0.53
NO_3^-	102	5	9	5.2	0.7	50	50	0.28	5.08	<0.001 *
SO_4	102	3	14	4.5	1.8	250	250	0.07	1.39	0.16
Cl	102	6	42	9.9	4.8	250	250	0.16	3.20	0.001 *
Fe^{2+}	102	10	142	21	22.4	200	200	0.12	2.29	0.02 **
Mn^{2+}	102	<3	<3	3	0.1	50	400	−0.004	0.10	0.92
Ni	102	1	2	1.7	0.4	20	70	0.03	0.74	0.45

Note: pH—hydrogen ion concentration; TH—total hardness (given by the concentration of calcium ions (Ca^{2+}) and magnesium ions (Mg^{2+})); Na^+ —sodium; NO_3^- —nitrate; SO_4 —sulphate; Cl—chloride; Fe^{2+} —iron; Mn^{2+} —manganese; Ni—nickel; NS—National Standard; WHO GV—World Health Organization guidelines; * denotes $p < 0.05$; ** denotes $p < 0.01$, indicates the statistical significance of the Moran's test; z-score indicate statistical significance of clustering (it must be greater than 1.96 at $p < 0.05$ and greater than 2.58 at $p < 0.01$); p value probability of error in rejecting the null hypothesis.

2.3. Data Collection Procedure

In this study, first, the municipalities in Cilento with the highest concentrations of long-lived people, including old, nonagenarians, and centenarians, were identified through geomaps; second, the annual means of the most significant physicochemical, mineral and metal parameters of tap drinking water served this region were examined, evaluating data from municipalities fed by the same catchment sources. Elements with zero values were not evaluated; the parameters were then geomapped and clustered to assess their significance at the spatial level; finally, the influence that the different properties of tap drinking water had on longevity was highlighted through ordinary least squares (OLS) and geographically weight regression (GWR) models.

2.4. Statistical Analysis

This study used STATA software [48] for descriptive statistics and to calculate longevity indicators based on data from the Cilento Municipal Archives 2021–2022 and the National Institute of Statistics 2022, as well as to calculate the annual means of physicochemical parameters of tap drinking water supplied by CONSAC and ASIS water service in Cilento. Before performing the statistical analysis, the Skewness and Kurtosis normality test was used to determine whether the data were normally distributed. QGIS 3.14.15 [49] was then used to produce spatial distribution maps of longevity and drinking water parameters. The global Moran's I index was used to describe the characteristics of the global spatial cluster value of the longevity index and water parameter (for Moran's formulas, see our previous study) [5], through ArcGIS [50]. To study the spatial relationship between the explanatory variables and the longevity outcome variables in the provided dataset, an OLS

regression model and a GWR model were used and analyzed with ArcGIS 10.8 software (Esri, Redlands, CA, USA).

3. Results

3.1. Geographical Distribution of Old, Nonagenarians and Centenarians in Cilento Region

Based on the new longevity population data (Table 1 and Figure 1a–d), we confirmed what was previously reported in our research [5]; namely, that the distribution of old, nonagenarians and centenarians was clearly delineated in the north–central and southeastern municipalities of Cilento.

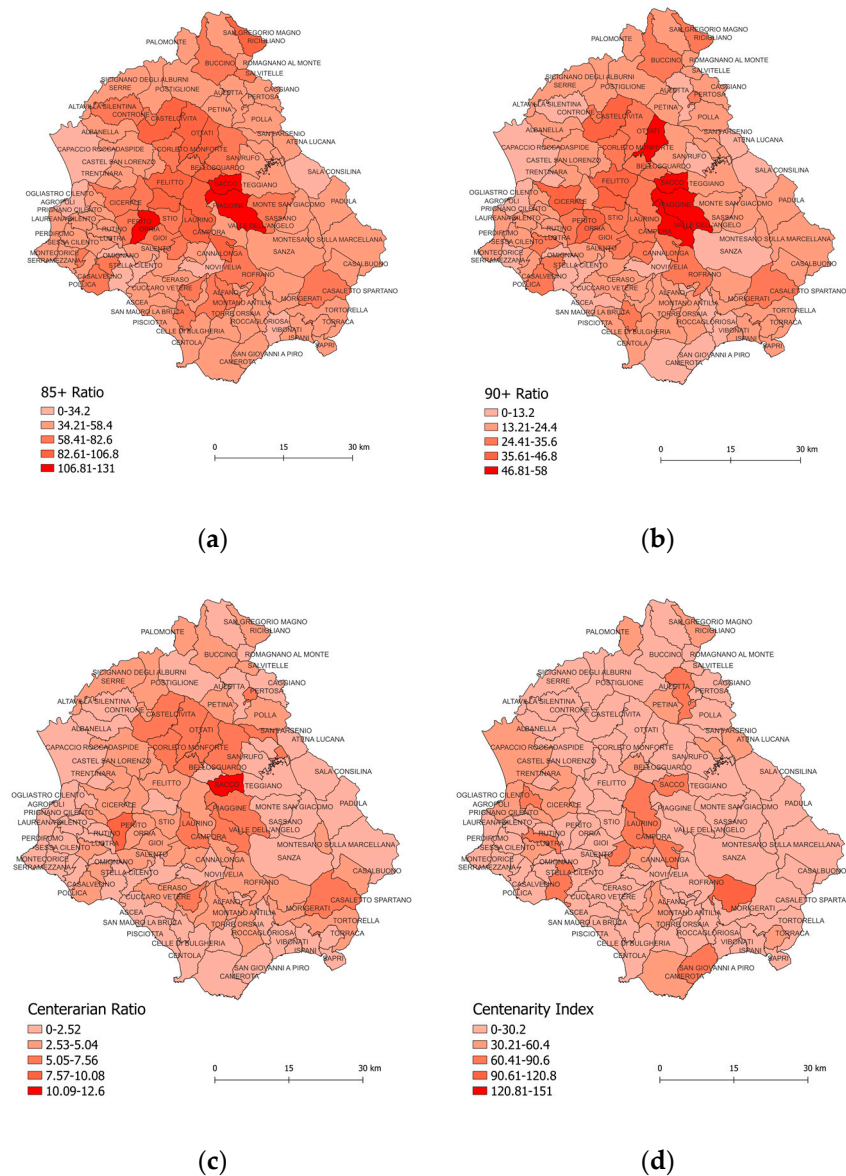


Figure 1. Spatial distribution of the four longevity indices in Cilento municipalities. Note: (a) Spatial distribution of 85+ ratio; (b) Spatial distribution of 90+ ratio; (c) Spatial distribution of centenarian ratio; (d) Spatial distribution of centenarity index.

The highest 85+ ratio was recorded in Sacco (13.1), Orria (10.9), Piaggine (10.9), Campora (10.6), and Magliano Vetere (10.3), while the lowest was recorded in Capaccio (1.0), Casal Velino (1.0), Novi Velia (2.5), and Agropoli (3.2) (Figure 1a).

The highest 90+ ratio was recorded in Sant'Angelo a Fasanella (5.8), Sacco (5.7), Valle dell'Angelo (5.3), Piaggine (4.9), while the lowest was recorded in Capaccio (0.2), Casal Velino (0.2), Novi Velia (0.9), Castelnuovo Cilento (1) (Figure 1b).

The highest centenarian ratio was recorded in Sacco (12.6), Perito Cilento (7.7), Pertosa (7.4), Campora (7.1), Sant'Angelo a Fasanella (7), Bellosguardo (6.7), while the lowest indices were recorded in Alfano (0), Romagnano al Monte (0), Rutino (0), Roscigno (0.1), Novi Velia (0.3), and Giungano (0.6) (Figure 1c).

The highest CI% was recorded in Caselle in Pittari (9.3), Campora (8.3), Sacco (7.7), Moio della Civitella (7.1), while the lowest was reported for Albanella (0), Alfano (0), Casalbuono (0), Casaletto Spartano (0) (Figure 1d).

Thus, we were able to state that the longevity indicators, according to the global auto-correlation values, were spatially clustered more than would be expected if the underlying spatial processes were random, so we rejected the null hypothesis. In fact, Moran's Z-score I values indicated spatial autocorrelation at the 0.01 significance level for the 85+ ratio and for the 90+ ratio. No significance level was found for the centenarian ratio and centenarity index values (Table 1).

3.2. Trace Elements Concentration in Tap Drinking Water

The descriptive statistics and spatial distribution of the tap water elements of the Cilento municipalities are shown in Table 2 and Figure 2a–j, respectively.

The tap drinking water in the 102 municipalities of Cilento falls within the WHO definition of fresh water [15].

First of all, the water pH values in the various Cilento municipalities ranged from 7.4 to 8.3, which meant that the drinking water of this Southern region of Italy was all alkaline, and differentiated by the weakly to strongly alkaline level (Figure 2a). The municipalities with a higher concentration of long-lived people had an alkalinity level between 7.9 and 8.2.

The TH (given by the concentration of Ca^{2+} and Mg^{2+}) [32] of tap drinking water ranged from 9.6 °F to 34.8 °F, which means that the water varied between soft water (TH = 7–15 °F) and hard water (TH = 25–35 °F) (Figure 2b).

The TDS showed differences in levels among the 102 Cilento municipalities, with drinking water values ranging from excellent to poor (Figure 2c).

The concentrations of Na^+ , NO_3^- , SO_4 and Cl_- showed minimal spatial differences among the 102 Cilento municipalities (Figure 2d–g), and, as for heavy metals, no traces of arsenic, lead, mercury, cadmium were detected; only Ni was evident, with a minimum concentration of 1.7 µg/L out of the 20 µg/L recommended by National Standard (NS) and 70 µg/L recommended by World Health Organization guidelines (WHOGV) (Figure 2j). Copper was nil, while Mn had a mean concentration of 3 µg/L compared with the 50 µg/L recommended by NS and 400 µg/L established by WHOGV (Figure 2i). The highest concentrations of iron were found in areas not inhabited by the long-lived (Figure 2h). The concentrations of all elements were well below the recommended standards (Table 2). In fact, tap water quality in Cilento municipalities was evaluated according to recommended standards, both national [45,46] and World Health Organization [15]. As a result of this assessment, all drinking water in Cilento can be considered of good quality.

In addition, Moran’s I index was used to test for the presence of spatial autocorrelation and to identify whether case densities were randomly distributed in the study area. We found that longevity densities were clustered according to certain elements of tap drinking water, such as water pH ($p = 0.004$), TDS ($p = 0.003$), iron ($p = 0.02$), nitrate ($p < 0.001$), chloride ($p = 0.001$).

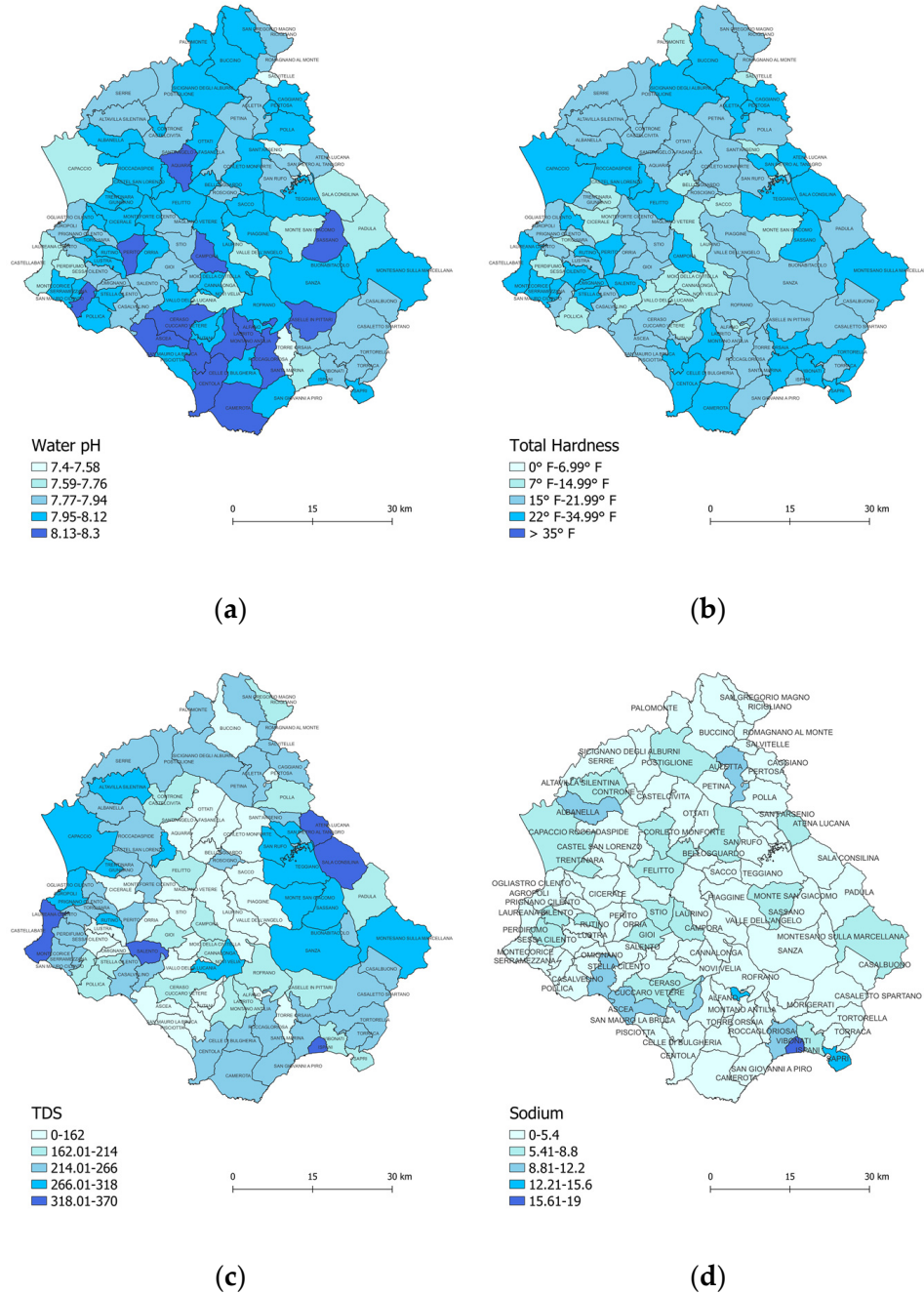


Figure 2. Cont.

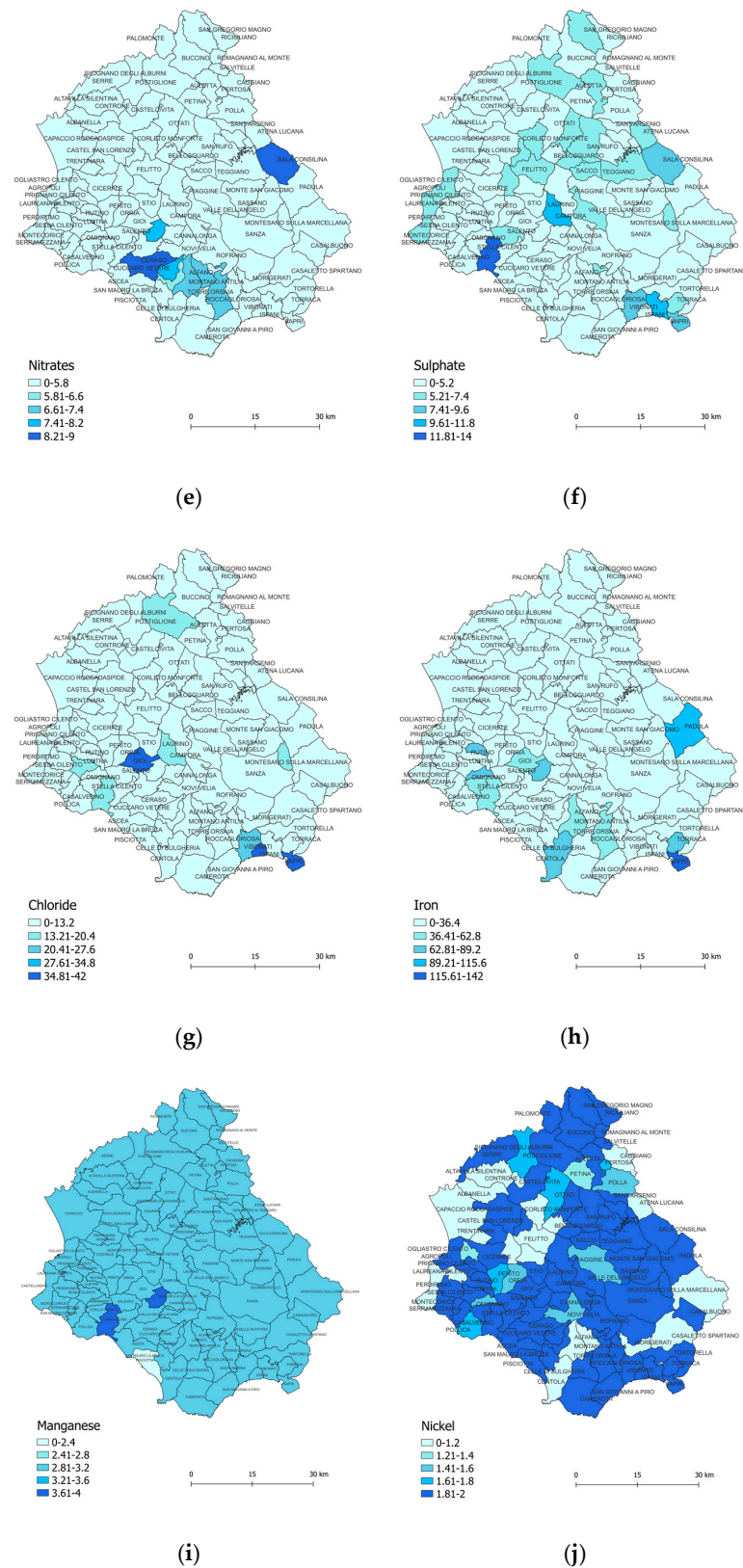


Figure 2. Spatial distribution by Cilento municipalities of tap drinking water elements. Note: (a) Spatial distribution of water pH; (b) Spatial distribution of total hardness TH; (c) Spatial distribution of total dissolved solids TDS; (d) Spatial distribution of sodium; (e) Spatial distribution of nitrates; (f) Spatial distribution of sulphate; (g) Spatial distribution of chloride; (h) Spatial distribution of iron; (i) Spatial distribution of manganese; (j) Spatial distribution of nickel.

3.3. Relationship between Tap Drinking Water Elements and Longevity

OLS and GWR regression models were used to evaluate the relationship between longevity and tap water elements (Table 3 and Figure 3a–j, respectively). OLS regression results showed a negative relationship with TH, TDS, sodium and iron for both the 85+ ratio and 90+ ratio. In addition, a negative relationship was found with nickel for the 85+ ratio, while a positive relationship was found with chloride for the 90+ ratio. The centenarian ratio also had a negative relationship with TH, TDS, sodium and iron, and a positive association with chloride. Finally, the centenarity index showed a positive correlation with manganese.

Table 3. Results of OLS regression.

Longevity Indicators	Tap Drinking Water Elements	Coefficient	t	p Value
Model 1 (R ² 0.32 AICc 906.91) 85+ ratio	Water pH	2.76	0.24	0.79
	TH	−4.83	−2.81	0.005 **
	TDS	−0.22	−6.33	<0.001 **
	Sodium	−1.77	−1.90	0.03*
	Nitrates	−1.15	−0.46	0.50
	Sulphate	2.23	1.86	0.17
	Chloride	0.53	0.95	0.28
	Iron	−0.22	−2.60	0.002 **
	Manganese	−7.71	−0.65	0.51
	Nickel	−7.56	−1.54	0.04 *
Model 2 (R ² 0.37 AICc 754.28) 90+ ratio	Water pH	9.50	1.58	0.11
	TH	−1.79	−1.86	0.004 **
	TDS	−0.10	−6.14	<0.001 **
	Sodium	−1.34	−3.04	0.002 **
	Nitrates	−0.95	−0.80	0.42
	Sulphate	0.83	1.45	0.26
	Chloride	0.54	2.05	0.02 *
	Iron	−0.09	−2.24	0.02 *
	Manganese	0.71	0.12	0.93
	Nickel	−2.30	−0.98	0.32
Model 3 (R ² 0.25 AICc 407.77) Centenarian ratio	Water pH	−0.38	−0.38	0.70
	TH	−0.23	−1.52	0.009 **
	TDS	−0.01	−4.33	0.009 **
	Sodium	−0.21	−2.61	0.002 **
	Nitrates	0.20	0.92	0.35
	Sulphate	0.13	1.28	0.20
	Chloride	0.10	2.04	0.005 **
	Iron	−0.02	−2.69	0.004 **
	Manganese	0.83	0.80	0.42
	Nickel	−0.67	−1.55	0.12
Model 4 (R ² 0.15 AICc 960.91) Centenarity index	Water pH	16.63	1.13	0.26
	TH	−1.74	−0.78	0.43
	TDS	−0.02	−0.57	0.51
	Sodium	−1.09	−0.91	0.36
	Nitrates	−2.67	−0.36	0.71
	Sulphate	1.59	1.02	0.30
	Chloride	0.39	0.54	0.58
	Iron	−0.06	−0.54	0.58
	Manganese	50.01	3.27	0.001 **
	Nickel	2.30	0.36	0.71

Note: * significant p value ≤ 0.05; ** significant p value ≤ 0.01; Model 1–4 indicate the models analyzed with OLS; R² indicates R-squared, coefficient of determination; AICc—Akaike’s Information Criterion; TH—total hardness; TDS—total dissolved solids; OLS—ordinary least squares.

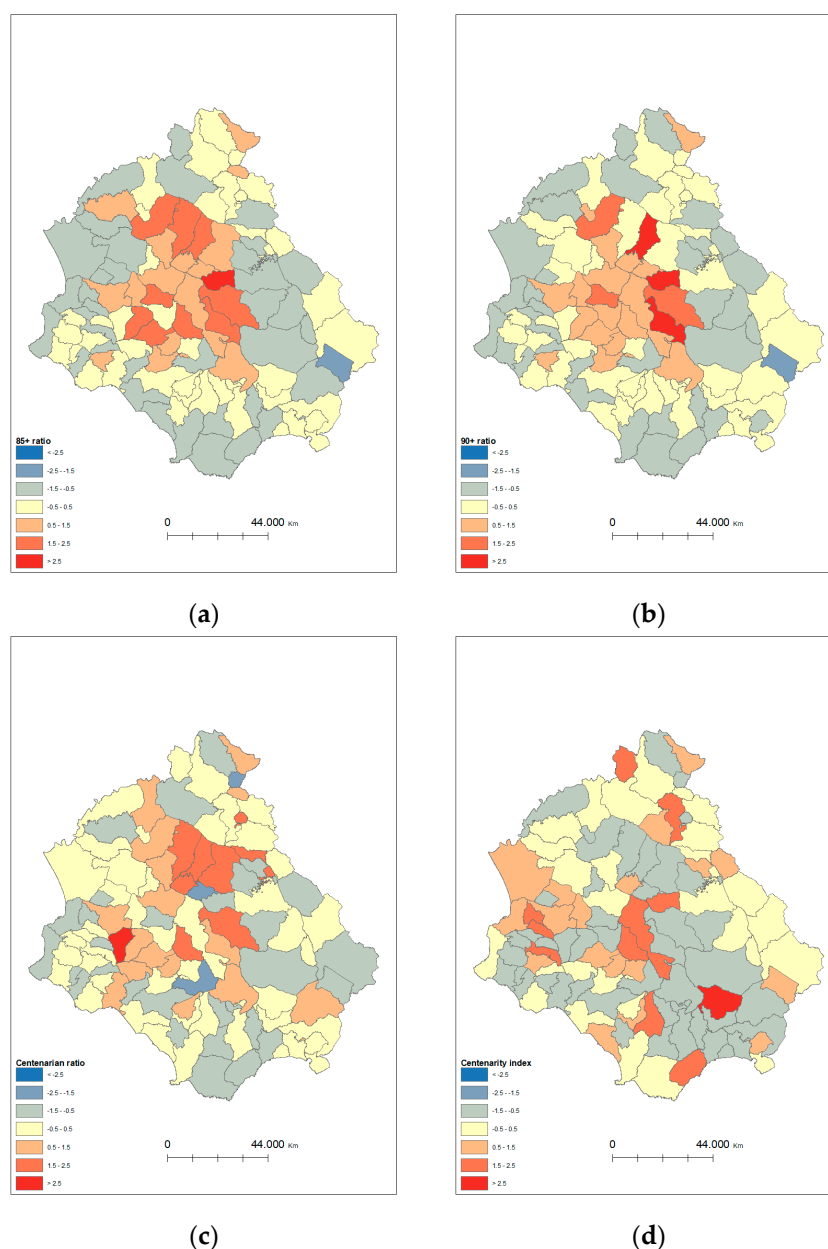


Figure 3. Results of the GWR models for 85+ ratio, 90+ ratio, centenarian ratio and centenarity index showing the local R2. Note: (a) local R2 for 85+ ratio; (b) local R2 for 90+ ratio; (c) local R2 for centenarian ratio; (d) local R2 for centenarity index. GWR—geographically weight regression.

For the GWR models, shown in Figure 3a–j; all OLS regression variables were used.

4. Discussion

In the present study, the relationship between the physicochemical elements of drinking water and longevity in Cilento was investigated. Based on the results, several elements emerged to support our hypothesis that drinking water in Cilento region can affect health and longevity.

Water is essential for hydration and, thus, for life; in fact, in the human body, thanks to its special properties, numerous vital functions can take place regularly and provide benefits [13]. The main purpose of a drinking water supply is to protect human health, to restore lost health to those suffering from conditions such as hypertension, diabetes and other chronic diseases, and to prevent dehydration, which is associated with increased disability in the old [51,52].

The beneficial properties of water have also been highlighted by studies conducted on the long-lived Hunza people [53,54], whose longevity was due not only to their simple and healthy lifestyle, but also to the use of water with a high pH level. Cilento, as our results showed, was characterized by both the presence of nonagenarians and centenarians, and by the presence of alkaline drinking water in all 102 municipalities. Indeed, what differentiates the municipalities was the weakly to strongly alkaline level of drinking water. Municipalities with a higher concentration of long-lived people had a higher alkalinity level, ranging from 7.9 to 8.2, than those without long-lived people (ranging from 7.4 to 7.8). In addition, the Moran I index showed that longevity density is significantly correlated with water pH. This result is in agreement with Jin et al. [27], who confirmed that hydrogen-rich functional water has been introduced as a therapeutic strategy for health promotion and disease prevention. Other studies in animal models have shown positive effects, improving body weight and offspring development [25,26] with the use of alkaline water. In addition, several biological effects have been documented, such as antidiabetic and antioxidant actions [27], DNA-protective effects [28], and growth-promoting activities [26]. Further confirmations of our findings come from Magro et al., who conducted a 3 year survival study on 150 mice, in which the biological effects of alkaline water consumption were investigated in depth. The results showed that the mice experienced benefits in longevity in terms of the “aging deceleration factor” [55].

An important etiological factor worldwide is hard water (sum of Ca^{2+} and Mg^{2+}), which causes many diseases such as cardiovascular problems, diabetes, kidney dysfunction, and neural diseases. According to our results, water varied between soft and medium-hard in the Cilento municipalities that hosted the long-lived groups; the regression outcome showed a significant inverse relationship between the long-lived (85+ ratio, 90+ ratio, Centenarian ratio) and hard water. In agreement with our results, many studies have reported an inverse relationship between drinking water hardness and cardiovascular disease [12,56–59], or a weak inverse relationship between risk factors such as hypertension, smoking habit, and elevated serum lipids [60,61].

Regarding the statistically significant results for Total Dissolved Solids, which refer to the total dissolved substances in drinking water that confer a bitter or salty taste to the water, the values of tap drinking water varied from excellent to poor, with differences in levels among the 102 municipalities in Cilento. Municipalities with the lowest TDS, such as Sacco, Cuccaro Vetere, Pertosa, San’Angelo a Fasanella, Bellosguardo, Piaggine, and others, had excellent water levels and higher concentrations of long-lived people.

Drinking water is a major contributor to daily sodium intake, but in areas where there are large concentrations of salinity, this can become a risk factor for hypertension [62]. In Cilento, the highest sodium concentrations were found mainly in the northwestern and southwestern areas, while the central areas, where the long-lived were concentrated, had lower amounts of sodium. Low-sodium drinking water sources in Cilento could help prevent hypertension-related morbidity and mortality for the large number of people living in these areas, evidence that is in line with the significant inverse results of our regression. Moreover, these results agreed with the study of Sacks et al. [63], in which it was reported that with the reduction in sodium intake from high (3.6 g/day) to intermediate (2.3 g/day) in the control group, systolic blood pressure decreased by 2.1 mm Hg, and further reductions in sodium intake from intermediate to low led to a further reduction in blood pressure of 4.6 mm Hg. Systematic reviews and meta-analyses of randomized controlled trial (RCT) studies have reported links between high sodium intake and increased blood pressure in the population [64–66]. Excessive sodium intake is also directly associated with stroke [67] and elevated levels of inflammatory markers [68,69]. Reduced sodium intake is associated with improved renal function, reduced arterial stiffness, and vasodilation of small blood vessels [70].

Iron was present with consistent values throughout Cilento, with a higher value toward the southwestern coastal area outside the longevity area, and was significantly clustered and inversely correlated with local longevity (85+ ratio, 90+ ratio, and centenarian

ratio). These results indicate that iron is an essential trace element for life, but can generate toxicity under overloaded conditions. According to Baschant et al. [71], the accumulation of iron in organs and tissues, if untreated or poorly controlled, can lead to complications such as liver cirrhosis, heart failure or diabetes.

In Cilento, with regard to heavy metals in the water, no traces of arsenic, lead, mercury, cadmium, and copper were detected, but only nickel was evident, with a minimum concentration of 1.7 µg/L, a parameter well below the values recommended not only by NS and WHOGV but also by the European Food Safety Authority, which established a tolerable daily intake (TDI) of 13 µg/L body weight. According to data reported in the United States on tap drinking water, nickel concentrations ranged from 0.55 to 25 µg/L; in Australia, nickel concentrations in drinking water were generally <10 µg/L [72], and, according to European Food Safety Authority (EFSA), which evaluated the results of several European surveys on nickel in drinking water, the mean lower and upper limits for all samples was 2 and 3 µg/L, respectively [73]. These data confirm that the value of nickel in Cilento tap drinking water is lower than the concentrations reported in other nations and does not pose a health risk.

Of note, a trend of positive association was observed between manganese in Cilento tap drinking water and the centenarity index. This result is in agreement with the US National Research Council (NRC), which has established a safe and adequate dietary intake (ESADDI) of 2–5 mg/day of Mn for adults [74]. Furthermore, Mn in humans is known to vary with life stage and sex [75], becoming essential during old age. Herein, Mn is an essential nutrient required for a number of metabolic functions, including those involved in energy metabolism, immune system improvement, nervous system function, blood coagulation and the activity of antioxidant enzymes that protect cells from free radical damage [76].

On the basis of the data, this study has some limitations. First, longevity is the result of a combination of genes, the natural environment and socioeconomic status. Therefore, other factors could interfere with the relationship between the water environment and longevity. Second, it is not known whether the conclusions obtained in the Cilento region can be applied to other longevity areas, due to their different geological conditions, climate, etc. Therefore, it is of great importance to study the effects of tap drinking water on longevity based on the common characteristics of drinking water quality in multiple longevity areas. Furthermore, we did not evaluate the influence of Cilento tap water on common diseases in the region. In addition, the water monitoring data provided by the Cilento Water Service Company lacked some trace elements, such as potassium, zinc, and individual calcium and magnesium data, as we only had data on overall water hardness (sum of Ca²⁺ and Mg²⁺).

Further research will be needed in the future to establish a holistic assessment between different areas of longevity in Cilento, tap water quality and common diseases in the region, including thorough in vivo research in mice.

5. Conclusions

In conclusion, we can say, to the best of our knowledge, that this is the first study to investigate the possible relationship between longevity in Cilento and the elements present in tap water at the municipal level. The results of the study confirmed that there is a high prevalence of old, nonagenarians and centenarians in Cilento, concentrated in the north-central and southeastern areas of the territory, and that some elements in tap drinking water may contribute to local longevity. In particular, drinking water in the 102 Cilento municipalities was found to be alkaline and falls within the WHO definition of fresh water. Regarding heavy metals, no traces of arsenic, lead, mercury, cadmium and copper were detected, but only minimal concentrations of nickel, iron and manganese, well below the NS and WHOGV recommended values. The municipalities with higher longevity concentrations had higher alkalinity levels than the other municipalities, soft to medium-hard water hardness, total dissolved solids equivalent to excellent water levels,

lower sodium concentrations, advantageous iron concentration, and an adequate dietary intake of manganese per day.

Author Contributions: Conceptualization, S.M.A., R.H.W.F., J.G., A.G., C.V., A.A.P. and M.C.; methodology, S.M.A.; software, S.M.A.; formal analysis, S.M.A.; data curation, S.M.A.; writing—original draft preparation, S.M.A.; review and editing, S.M.A. and E.C.; visualization, J.G. and A.G.; supervision, R.H.W.F., C.V., A.A.P. and M.C.; project administration, S.M.A. and M.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical approval from the Human Research Ethics Committee was not required for this study. Our study exploited the demographic database of Official Archives. This represents a retrospective study and is not directly associated with patients.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data included in this manuscript were provided by the National Institute of Statistics and the Cilento Municipal Archives for populations; and by the official Integrated Water Service Providers in the Cilento area for water. Therefore, we are not authorized to share the data with third party organizations. However, the corresponding author is available to provide any explanation to the Editor if requested.

Acknowledgments: Thanks are given to the staff of CONSAC, especially Eng. Enzo Tambasco, and to the staff of ASIS, respectively entities managing water service in Cilento, for their active cooperation. Special thanks to graduate student Antonio Pio Montefusco for technical support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Dato, S.; Crocco, P.; D'Aquila, P.; de Rango, F.; Bellizzi, D.; Rose, G.; Passrino, G. Exploring the role of genetic variability and life style on oxidative stress response for healthy aging and longevity. *Int. J. Mol. Sci.* **2013**, *14*, 16443–16472. [[CrossRef](#)] [[PubMed](#)]
2. Vecchione, C.; Villa, F.; Carrizzo, A.; Spinelli, C.C.; Damato, A.; Ambrosio, M.; Ferrario, A.; Madonna, M.; Uccellatore, A.; Lupini, S.; et al. A rare genetic variant of BPIFB4 predisposes to high blood pressure via impairment of nitric oxide signaling. *Nat. Sci. Rep.* **2019**, *7*, 9706. [[CrossRef](#)] [[PubMed](#)]
3. Montella, F.; Lopardo, V.; Cattaneo, M.; Carrizzo, A.; Vecchione, C.; Ciaglia, E.; Puca, A.A. The Role of BPIFB4 in Immune System and Cardiovascular Disease: The Lesson from Centenarians. *Transl. Med. UniSa* **2021**, *24*, 1–12. [[CrossRef](#)] [[PubMed](#)]
4. Feng, Z.; Lin, M.; Wu, R. The regulation of aging and longevity: A new and complex role of p53. *Genes Cancer* **2011**, *2*, 443–452. [[CrossRef](#)] [[PubMed](#)]
5. Aliberti, S.M.; De Caro, F.; Funk, R.H.W.; Schiavo, L.; Gonnella, J.; Boccia, G.; Capunzo, M. Extreme Longevity: Analysis of the Direct or Indirect Influence of Environmental Factors on Old, Nonagenarians, and Centenarians in Cilento, Italy. *Int. J. Environ. Res. Public Health* **2022**, *19*, 1589. [[CrossRef](#)]
6. Azin, A.L.; Zeldi, I.P.; Smirnov, A.V.; Shagibalov, R.Z. Aging and longevity as indicators of ecological health of the environment. *Russ. J. Ecol.* **2001**, *32*, 216–219. [[CrossRef](#)]
7. Aliberti, S.M.; Funk, R.H.W.; Schiavo, L.; Giudice, A.; Ciaglia, E.; Puca, A.A.; Gonnella, J.; Capunzo, M. Clinical Status, Nutritional Behavior, and Lifestyle, and Determinants of Community Well-Being of Patients from the Perspective of Physicians: A Cross-Sectional Study of Young Older Adults, Nonagenarians, and Centenarians in Salerno and Province, Italy. *Nutrients* **2022**, *14*, 3665. [[CrossRef](#)]
8. Darviri, C.; Demakakos, P.; Tigani, X.; Charizani, F.; Tsiou, C. Psychosocial dimensions of exceptional longevity: A qualitative exploration of centenarians' experiences, personality, and Life strategies. *Int. J. Aging Hum. Dev.* **2009**, *69*, 101–118. [[CrossRef](#)]
9. Pizza, V.; Antonini, P.; Marino, R.; D'Arena, G.; Lucibello, S.G.; Rizzo, M.; Brenner, D.A.; Jeste, D.V.; Di Somma, S. Cognitive Health of Nonagenarians in Southern Italy: A Descriptive Analysis from a Cross-Sectional, Home-Based Pilot Study of Exceptional Longevity. *Medicina* **2020**, *56*, 218. [[CrossRef](#)]
10. Waddington, C.H. The epigenotype. *Endeavour* **1942**, *1*, 18–21. [[CrossRef](#)]
11. Selinus, O.; Alloway, B.; Centeno, J.A.; Finkelman, R.B.; Fuge, R.; Lindh, U.; Smedley, P. *Essentials of Medical Geology—Impacts of the Natural Environment on Public Health*; Elsevier: New York, NY, USA, 2016.
12. Sengupta, P. Potential Health Impacts of Hard Water. *Int. J. Prev. Med.* **2013**, *4*, 866–875. [[PubMed](#)]
13. Funk, R.H.W. Understanding the Feedback Loops between Energy Matter Life. *Front. Biosci.* **2022**, *14*, 29. [[CrossRef](#)] [[PubMed](#)]

14. ISS—Istituto Superiore di Sanità. Clima, Ambiente e Salute. *Istituto Superiore di Sanità* 24 January 2022. Available online: https://www.iss.it/clima-ambiente-salute/-/asset_publisher/w4Y3CVICKYyo/content/id/5254546 (accessed on 19 December 2022).
15. World Health Organization (WHO). Guidelines for Drinking-Water Quality. World Health Organization, Geneva, 2011. 4th ed. Available online: https://apps.who.int/iris/bitstream/handle/10665/44584/9789241548151_eng.pdf (accessed on 10 November 2022).
16. Keller, W.D. Drinking water: Geochemical factor in human health. *Geol. Soc. Am. Bull.* **1978**, *89*, 334–336. [[CrossRef](#)]
17. Podgorski, J.; Berg, M. Global threat of arsenic in groundwater. *Science* **2020**, *368*, 845–850. [[CrossRef](#)] [[PubMed](#)]
18. Sarvestani, R.A.; Aghasi, M. Health risk assessment of heavy metals exposure (lead, cadmium, and copper) through drinking water consumption in Kerman city, Iran. *Environ. Earth Sci.* **2019**, *78*, 714. [[CrossRef](#)]
19. Srivastava, S.; Flora, S. Fluoride in drinking water and skeletal fluorosis: A review of the global impact. *Curr. Environ. Health Rep.* **2020**, *7*, 140–146. [[CrossRef](#)]
20. Kurtz, T.W.; Morris, R.C., Jr. Dietary chloride as a determinant of “sodium-dependent” hypertension. *Science* **1983**, *222*, 1139–1141. [[CrossRef](#)]
21. Luft, F.C.; Zemel, M.B.; Sowers, J.A.; Fineberg, N.S.; Weinberger, M.H. Sodium bicarbonate and sodium chloride: Effects on blood pressure and electrolyte homeostasis in normal and hypertensive man. *J. Hypertens.* **1990**, *8*, 663–670. [[CrossRef](#)]
22. McCallum, L.; Lip, S.; Padmanabhan, S. The hidden hand of chloride in hypertension. *Pflug. Arch.* **2015**, *467*, 595–603. [[CrossRef](#)]
23. Nerbrand, C.; Svärdsudd, K.; Ek, J.; Tibblin, G. Cardiovascular mortality and morbidity in seven counties in Sweden in relation to water hardness and geological settings. The project: Myocardial infarction in mid-Sweden. *Eur. Heart J.* **1992**, *13*, 721–727. [[CrossRef](#)]
24. Dore, M.P.; Parodi, G.; Portoghese, M.; Errigo, A.; Pes, G.M. Water Quality and Mortality from Coronary Artery Disease in Sardinia: A Geospatial Analysis. *Nutrients* **2021**, *13*, 2858. [[CrossRef](#)] [[PubMed](#)]
25. Watanabe, T.; Shirai, W. Influence of alkaline ionized water on reproductive functions in the rat. *Int. J. Fertil. Steril.* **1990**, *35*, 748–751.
26. Watanabe, T. Effect of alkaline ionized water on reproduction in gestational and lactational rats. *J. Toxicol. Sci.* **1995**, *20*, 135–142. [[CrossRef](#)] [[PubMed](#)]
27. Jin, D.; Ryu, S.H.; Kim, H.W.; Yang, E.J.; Lim, S.J.; Ryang, Y.S.; Chung, C.H.; Park, S.K.; Lee, K.J. Anti-diabetic effect of alkaline-reduced water on OLETF rats. *Biosci. Biotechnol. Biochem.* **2006**, *70*, 31–37. [[CrossRef](#)] [[PubMed](#)]
28. Shirahata, S.; Kabayama, S.; Nakano, M. Electrolyzed-reduced water scavenges active oxygen species and protects DNA from oxidative damage. *Biochem. Biophys. Res. Commun.* **1997**, *234*, 269–274. [[CrossRef](#)]
29. Hao, Z.; Liu, Y.; Li, Y.; Song, W.; Yu, J.; Li, H.; Wang, W. Association between longevity and element levels in food and drinking water of typical Chinese longevity area. *J. Nutr. Health Aging* **2016**, *20*, 897–903. [[CrossRef](#)]
30. Liu, Y.L.; Luo, K.L.; Lin, X.X.; Gao, X.; Ni, R.X.; Wang, S.B.; Tian, X.L. Regional distribution of longevity population and chemical characteristics of natural water in Xinjiang, China. *Sci. Total Environ.* **2014**, *473–474*, 54–62. [[CrossRef](#)]
31. Li, X.; Liu, Z.; Yao, Y.; Yu-Mei, L.; Dong-Mei, G.; Ju, W.; Guan-Rui, W.; Li, Z.; Xi-bao, G. Comparison of the mineral elements in drinking water between Mengshan longevity district and Jinan city. *Trace Elem. Electrolytes* **2016**, *33*, 116–119. [[CrossRef](#)]
32. Liu, Y.; Yuan, Y.; Luo, K. Regional distribution of Longevity population and Elements in drinking water in Jiangjin district, Chongqing City, China. *Biol. Trace Elem. Res.* **2018**, *184*, 287–299. [[CrossRef](#)]
33. Moretti, C.H.; Schiffer, T.A.; Montenegro, M.F.; Larsen, F.J.; Tsarouhas, V.; Carlström, M.; Samakovlis, C.; Weitzberg, E.; Lundberg, J.O. Dietary nitrite extends lifespan and prevents age-related locomotor decline in the fruit fly. *Free Radic. Biol. Med.* **2020**, *20*, 860–870. [[CrossRef](#)]
34. Carvalho, L.R.R.A.; Guimaraes, D.D.; Flor, A.F.L.; Leite, E.G.; Ruiz, C.R.; de Andrade, J.T.; Monteiro, M.M.O.; Balarini, C.M.; de Lucena, R.B.; Sandrim, V.C.; et al. Effects of chronic dietary nitrate supplementation on longevity, vascular function and cancer incidence in rats. *Redox Biol.* **2021**, *48*, 102209. [[CrossRef](#)] [[PubMed](#)]
35. Ente Parco Nazionale del Cilento, Vallo di Diano e degli Alburni. Geomorfologia e Geologia. Available online: <http://www.cilentoediano.it/it/geomorfologia-geologia> (accessed on 17 October 2022).
36. Gambino, R.; Nicoletti, D.; Rossi, F.; Blasi, C.; Milone, M.; Pasca, R.; Quaranta, G.; Cillo, B.; Coppola, P.; Amendol, A.; et al. Parco Nazionale del Cilento e Vallo di Diano. Relazione illustrativa. Regione Campania, Giunta Regionale–delibera n. 617 del 13 aprile 2007. Available online: <http://www.cilentoediano.it/it/piano-del-parco> (accessed on 10 October 2022).
37. CONSAC Gestioni Idriche spa. Water service in the Cilento area. Via Ottavio Valiante 30, 84078 Vallo della Lucania, Salerno, Italy. Available online: <https://www.consac.it/> (accessed on 30 December 2022).
38. Aliberti, S.M. Produzioni locali e tradizione gastronomica: Recupero e valorizzazione. In *Tra Vulnerabilità e Resilienza. Immagini di Transizione Socio-Ecologica in un'area della Campania*; Ammaturo, N., Ed.; Loffredo Editore: Napoli, Italy, 2012.
39. ISTAT. *Popolazione Residente 2020. Regioni e Comuni*; Istituto Nazionale di Statistica: Roma, Italy, 2021; Available online: http://dati.istat.it/Index.aspx?DataSetCode=DCIS_POPRES1 (accessed on 17 September 2022).
40. Lv, J.; Wang, W.; Li, Y. Effects of environmental factors on the longevous people in China. *Arch. Gerontol. Geriatr.* **2011**, *53*, 200–205. [[CrossRef](#)] [[PubMed](#)]
41. Roli, G.; Samoggia, A.; Miglio, R.; Rettaroli, R. Longevity pattern in the Italian region of Emilia Romagna: A dynamic perspective. *Geospat. Health* **2012**, *6*, 233–245. [[CrossRef](#)] [[PubMed](#)]

42. Robine, J.M.; Caselli, G. An unprecedented increase in the number of centenarians. *Genus* **LXI** **2005**, *61*, 57–82.
43. Magnolfi, S.; Petrucci, E.; Pinzani, P.; Malentacchi, F.; Pazzagli, M.; Antonini, F.M. Longevity index (LI%) and centenarity index (CI%): New indicators to evaluate the characteristics of aging process in the Italian population. *Arch. Gerontol. Geriatr.* **2007**, *44*, 271–276. [[CrossRef](#)] [[PubMed](#)]
44. ASIS Salernitana Reti e Impianti. Water Service in the Cilento Area. Via Tommaso Prudenza CPS, 12, 84131 Salerno, Italy. Available online: <https://www.asisnet.it/> (accessed on 30 December 2022).
45. Ministero Della Salute. I Parametri di Qualità Delle Acque. Ministero Della Salute 6 October 2022. Available online: https://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=4464&area=acque_potabili&menu=controlli (accessed on 10 November 2022).
46. Gazzetta Ufficiale Della Repubblica Italiana. Qualità Delle Acque Destinate al Consumo Umano. Decreto Legislativo 2 February 2011, n. 31. Available online: <https://www.gazzettaufficiale.it/eli/id/2001/03/03/001G0074/sg> (accessed on 10 November 2022).
47. Gazzetta Ufficiale della Repubblica Italiana. Testo Unico Ambientale. Decreto Legislativo April 3, 2006 n. 152 “Norme in Materia Ambientale” Updated to D.L. 77/2021. Available online: http://www.ambienterose.net/wp-content/uploads/2021/09/ambiente_rosa_consulenze_ambientali_riorganizzazione_impresa_ex_231_T.U.A.-da-Leggi-dItalia.pdf (accessed on 10 November 2022).
48. STATA. StataCorp. *Stata Statistical Software*, Release 16.1; StataCorp MP: College Station, TX, USA, 2019.
49. QGIS. QGIS 2019. Geographic Information System; Release 3.14.15; Standalone Installer, Open Source. Available online: <https://www.filehorse.com/download-qgis/53872/?amp> (accessed on 10 November 2022).
50. ArcGIS. ArcGIS Desktop 2019. *Geospatial Processing Programs*, Release 10.8; Esri: Redlands, CA, USA, 2019.
51. Hooper, L.; Bunn, D.; Jimoh, F.O.; Fairweather-Tait, S.J. Water-loss dehydration and aging. *Mech. Ageing Dev.* **2014**, *136*, 50–58. [[CrossRef](#)]
52. Palma, L.; Marques, L.T.; Bujan, J.; Rodrigues, L.M. Dietary water affects human skin hydration and biomechanics. *Clin. Cosmet. Investig. Dermatol.* **2015**, *8*, 413–421.
53. Bircher, R.; Ponticelli, G. *Gli Hunza, un Popolo che Ignorava la Malattia*; Libreria Editrice Fiorentina: Florence, Italy, 1980; ISBN 88-89264-07-1.
54. Vlahchev, T.; Zhivkov, Z. Hunza—A healthy and a long living people. *Asklepii* **2022**, *15*, 96–97.
55. Magro, M.; Corain, L.; Ferro, S.; Baratella, D.; Bonaiuto, E.; Terzo, M.; Corraducci, V.; Salmaso, L.; Vianello, F. Alkaline Water and Longevity: A Murine Study. *Evid Based Complement. Alternat. Med.* **2016**, *2016*, 3084126. [[CrossRef](#)]
56. Anderson, T.W.; Neri, L.C.; Schreiber, G.B.; Talbot, F.D.; Zdrojewski, A. Letter: Ischemic heart disease, water hardness and myocardial magnesium. *Can. Med. Assoc. J.* **1975**, *113*, 199–203.
57. Masironi, R.; Pisa, Z.; Clayton, D. Myocardial infarction and water hardness in the WHO myocardial infarction registry network. *Bull. World Health Organ.* **1979**, *57*, 291–299. [[PubMed](#)]
58. Leoni, V.; Fabiani, L.; Ticchiarelli, L. Water hardness and cardiovascular mortality rate in Abruzzo, Italy. *Arch. Environ. Health* **1985**, *40*, 274–278. [[CrossRef](#)]
59. Kubis, M. Relation of water hardness to the occurrence of acute myocardial infarct. *Acta Univ. Palacki Olomuc Fac. Med.* **1985**, *111*, 321–324. [[PubMed](#)]
60. Lacey, R.F.; Shaper, A.G. Changes in water hardness and cardiovascular death rates. *Int J Epidemiol* **1984**, *13*, 18–24. [[CrossRef](#)] [[PubMed](#)]
61. Shaper, A.G.; Pocock, S.J.; Walker, M.; Cohen, N.M.; Wale, C.J.; Thomson, A.G. British regional heart study: Cardiovascular risk factors in middle-aged men in 24 towns. *Br. Med. J. (Clin. Res. Ed.)* **1981**, *283*, 179–186. [[CrossRef](#)] [[PubMed](#)]
62. Scheelbeek, P.F.D.; Chowdhury, M.A.H.; Haines, A.; Alam, D.S.; Hoque, M.A.; Butler, A.P.; Khan, A.E.; Mojumder, S.K.; Blangiardo, M.A.G.; Elliott, P.; et al. High concentrations of sodium in drinking water and raised blood pressure in coastal deltas affected by episodic seawater inundations. *Lancet Glob. Health* **2016**, *4*, S18. [[CrossRef](#)]
63. Sacks, F.M.; Svetkey, L.P.; Vollmer, W.M.; Appel, L.J.; Bray, G.A.; Harsha, D.; Obarzanek, E.; Conlin, P.R.; Miller, E.R.; Simons-Morton, D.G.; et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N. Engl. J. Med.* **2001**, *344*, 3–10. [[CrossRef](#)]
64. Aburto, N.J.; Ziolkovska, A.; Hooper, L.; Elliott, P.; Cappuccio, F.P.; Meerpohl, J.J. Effect of lower sodium intake on health: Systematic review and meta-analyses. *BMJ* **2013**, *346*, f1326. [[CrossRef](#)]
65. Matyas, E.; Jeitler, K.; Horvath, K.; Semlitsch, T.; Hemkens, L.G.; Pignitter, N.; Siebenhofer, A. Benefit assessment of salt reduction in patients with hypertension: Systematic overview. *J. Hypertens.* **2011**, *29*, 821–828. [[CrossRef](#)]
66. Dickinson, H.O.; Mason, J.M.; Nicolson, D.J.; Campbell, F.; Beyer, F.R.; Cook, J.V.; Williams, B.; Ford, G. Lifestyle interventions to reduce raised blood pressure: A systematic review of randomized controlled trials. *J. Hypertens.* **2006**, *24*, 215–233. [[CrossRef](#)]
67. Xie, J.X.; Sasaki, S.; Joossens, J.V.; Kesteloot, H. The relationship between urinary cations obtained from the INTERSALT study and cerebrovascular mortality. *J. Hum. Hypertens.* **1992**, *6*, 17–21. [[PubMed](#)]
68. Yilmaz, R.; Akoglu, H.; Altun, B.; Yildirim, T.; Arici, M.; Erdem, Y. Dietary salt intake is related to inflammation and albuminuria in primary hypertensive patients. *Eur. J. Clin. Nutr.* **2012**, *66*, 1214–1218. [[CrossRef](#)] [[PubMed](#)]

69. Salgado, E.; Bes-Rastrollo, M.; de Irala, J.; Carmona, L.; Gomez-Reino, J.J. High sodium intake is associated with self-reported rheumatoid arthritis: A cross sectional and case control analysis within the SUN cohort. *Medicine* **2015**, *94*, e0924. [[CrossRef](#)] [[PubMed](#)]
70. Cook, N.R.; Cutler, J.; Obarzanek, E.; Buring, J.; Rexrode, K.; Kumanyika, S.K.; Appel, L.J.; Whelton, P.K. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: Observational follow-up of the Trials of Hypertension Prevention (TOHP). *BMJ* **2007**, *334*, 885–888. [[CrossRef](#)]
71. Baschant, U.; Altamura, S.; Steele-Perkis, P.; Muckenhaler, M.U.; Spasic, M.V.; Hofbauer, L.C.; Steinbicker, A.U.; Rauner, M. Iron effects versus metabolic alterations in hereditary hemochromatosis driven bone loss. *Trends Endocrinol. Metab.* **2022**, *33*, 652–663. [[CrossRef](#)]
72. World's Health Organisation. Nickel in Drinking-Water. Background Document for Development of WHO Guidelines for Drinking-Water Quality. 2021. Available online: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/who-guidelines-for-drinking-water-quality-background-document-nickel-2021_public-review-version-pdf (accessed on 21 December 2022).
73. EFSA (European Food Safety Authority). Update of the risk assessment of nickel in food. *EFSA J.* **2020**, *18*, 6268. [[CrossRef](#)]
74. Sistrunk, S.C.; Ross, M.K.; Filipov, N.M. Direct effects of manganese compounds on dopamine and its metabolite Dopac: An in vitro study. *Environ. Toxicol. Pharmacol.* **2007**, *23*, 286–296. [[CrossRef](#)]
75. Finley, J.W.; Johnson, P.E.; Johnson, L.K. Sex affects manganese absorption and retention by humans from a diet adequate in manganese. *Am. J. Clin. Nutr.* **1994**, *60*, 949–955. [[CrossRef](#)]
76. Avila, D.S. Manganese in Health and Disease. *Met. Ions Life Sci.* **2013**, *13*, 199–227.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.