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# Determinants of All-Cause Mortality and Incidence of Cardiovascular Disease (2009 to 2013) in Older Adults: The Ikaria Study of the Blue Zones

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## Abstract

**Aim:** Ikaria Island (North-East Aegean, Greece) has been recognized as one of the places with the highest life expectancy around the world (the Blues Zones). Risk factors in relation to 4-year all-cause mortality and cardiovascular disease (CVD) incidence in elders were studied. **Methods:** From June to October 2009, 330 men and 343 women, aged 65 to 100 years, were enrolled, and in June to July 2013, they were reevaluated. **Results:** Age-standardized, gender-specific, all-cause mortality rate was 790 deaths per 10 000 inhabitants, and causes of death were CVD (36%), cancer (21%), infection (10%), respiratory disease (2%), and other (31%). Incidence of CVDwas 520 cases per 10 000 men inhabitants and 320 cases per 10 000 women ($P = .03$). Age, male gender, heart rate, urea levels, left atrial maximum volume, left ventricular hypertrophy, thyroid-stimulating hormone, and moderate to severe depression were positively associated with mortality, whereas left ventricular ejection fraction as well as coffee and tea drinking, fruit intake, and exclusive olive oil use were inversely associated with CVD. **Conclusion:** Heart function markers in addition to antioxidant dietary factors were placed in this puzzle of CVD morbidity.

### Keywords

elderly, coronary heart disease, cardiovascular function, biomarkers, lifestyle, diet

## Introduction

Since the beginning of humanity, people are looking for methods to extend their life span and their quality of living. Despite the extensive scientific research and the studies carried on, the "secrets" of longevity remain, more or less, unknown. Moreover, the majority of studies that have evaluated factors associated with mortality or the development of various diseases were performed among middle-aged people, but less is known whether these factors play a role in living beyond the expected life span. Recently, Ikaria Island, in eastern Aegean Sea, in Greece has been recognized as one of the places on the earth where people live much longer than other places.[1] Following this observation, the Ikaria Study was conducted in 2009 to illustrate biological, environmental, and lifestyle factors related to long living, and during the summer 2013, the 4-year follow-up was performed.

The aim of this work was to examine various anthropometric, sociodemographic, clinical, lifestyle characteristics, and well-known risk factors in relation to 4-year death rates of all-cause mortality and cardiovascular disease (CVD) in the Ikaria Study participants.

## Methods

### *Study Sample*

From June 2009 to October 2009, 673 individuals older than 65 years, permanent inhabitants from the above-mentioned area, were enrolled into the study (ie, 10% of the total population of the island). Of them, 343 were women and 330 were men. All participants were interviewed by trained personnel (cardiologists, general practitioners, and nurses) who used a standard questionnaire developed for the purpose of the study. The participants were recruited on a volunteer, feasibility basis from the general population and from all regions of the island, and people living in institutions were excluded from the sampling.

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### Bioethics

All participants were informed about the aims of the study and gave their written informed consent. The study was approved by the Ethics Committee of our institution and was carried out in accordance with the Declaration of Helsinki (1989).

### Sociodemographic and Lifestyle Measurements (Baseline)

The baseline evaluation included basic demographic items, such as age and gender, and anthropometric measurements, such as weight, height, and waist circumference, which were measured following standard procedures and various clinical and lifestyle characteristics.

### Physical Activity Assessment (Baseline)

Physical activity was evaluated using the shortened version of the self-reported International Physical Activity Questionnaire (IPAQ) validated for the Greek population.[2] Participants who did not report any physical activities or reported very low physical activity (ie, <600 metabolic equivalent/min/wk) were defined as physically inactive.

### Dietary Assessment (Baseline)

Dietary assessment was based on a validated and reliable food frequency questionnaire (FFQ) that has been developed especially for older people.[3] In brief, consumption of all main food groups (ie, red meat and meat products, fish and fish products, poultry, milk and other dairy products, fruits, vegetables and greens, cereals, as well as added lipids) and beverages was assessed in terms of daily, weekly, and monthly consumption. The overall assessment of dietary habits was evaluated through a special diet score, the MedDietScore (theoretical range, 0-55), which assesses the level of adherence to the Mediterranean dietary pattern.[4,5] Higher values of the score indicate greater adherence to this pattern and, consequently, healthier dietary habits.

### Assessment of Depressive Symptoms and Mental Status

Baseline symptoms of depression during the past month were assessed using the validated Greek translation of the shortened, self-report Geriatric Depression Scale (GDS; range, 0-15).[6] Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) translated in Greek language and consists of a list of questions, allowing a maximum score of 30.[7]

### Clinical and Biochemical Measurements

Fasting blood samples at baseline were collected from 08:00 to 10:00 hours. All the biochemical evaluation was carried out in the same laboratory that followed the criteria of the World Health Organization Reference Laboratories.[8]

### Electrocardiogram Measurements Designation

At baseline, all participants underwent digital electrocardiography (ECG), and a standard 12-lead ECG was recorded (10-second duration) by the use of SE-1010 PC ECG (EDAN Instruments, Inc). Smart ECG Measurement and Interpretation Program (SEMIP version 1.5) was used for the automated measurement and interpretation of ECG intervals.[9] Further details about the methods used in the baseline evaluation of the Ikaria Study may be found elsewhere.[10]

### Follow-Up

During June to July 2013, the investigators of the Ikaria Study performed the 4-year follow-up examination of the participants. Vital status was recorded for all participants (n = 676). In order to participate in the follow-up, all participants were appointed through telephone calls and then had face-to-face medical examination with the study's investigators. End points of the current study were (a) vital status (death from any cause), (b) development of coronary heart disease (CHD; ie, myocardial infarction, angina pectoris, other identified forms of ischemia—WHO-*ICD* coding 410-414.9, 427.2, 427.6—heart failure of different types, and chronic arrhythmias—WHO-*ICD* coding 400.0-404.9, 427.0-427.5, 427.9), or (c) development of stroke (WHO-*ICD* coding 430-438). Moreover, assessment of body weight and current lifestyle habits, including physical activity evaluation using the IPAQ score, dietary habits assessment using the same FFQ as the baseline examination, depression status using the GDS scale, and cognitive impairment level using the MMSE scale, and smoking status as well as current financial status (self-estimated as bad, moderate, good, and very good), and how this has affected the participants life choices and pharmaceutical treatment (in a nominal scale, ie, none, little, much, and very much), was performed.

### Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation. Categorical variables are presented as frequencies. Incidence rates of CVD (CHD as defined above or stroke) were calculated as the ratio of new cases to the number of people who participated in the follow-up. The independent samples *t* test or the analysis of variance was used for comparison between mean values of normally distributed continuous variables, after controlling for equality of variances (homoscedasticity), whereas the Mann–Whitney or the Kruskal–Wallis test was used for the skewed variables. Associations between categorical variables were tested by the $\chi^2$ test. Pearson or Spearman correlation coefficients were used, as appropriate, to test for correlations between continuous variables. The hazard ratios (HRs) of the investigated characteristics in relation to all-cause death, or developing a CVD event during the 4-year period, were estimated using Cox proportional hazards models. The time to event was recorded on an annual basis. Proportionality of the hazards was graphically tested. Interactions between sex and other covariates were tested, and when significant, they remained in the final model. Moreover, known confounders were also included in the model. The association between the investigated factors and the events is presented as the exponentials of the estimated model's coefficients, that is, HR and their corresponding 95% confidence intervals (CIs). Log-rank test was applied to evaluate significance of survival rates between groups of participants. All reported *P* values were based on 2-sided tests. All statistical calculations were performed using SPSS software (version 18.0; SPSS Inc, Chicago, Illinois).

## Results

### *Demographic and Clinical Characteristics at Baseline Examination*

In Table 1, the baseline characteristics regarding the investigated factors in men and women participants are presented.

### *Four-Year (2009 to 2013) All-Cause Mortality and CVD Incidence Rates Among the Ikaria Study Older Participants*

During 2009 to 2013, 53 deaths occurred in the study sample, that is, the all-cause mortality rate was 790 deaths per 10 000 inhabitants. The gender-specific, all-cause mortality rates were 580 per 10 000 women and 100 per 10 000 men inhabitants ($P = .04$). Causes of death were acute myocardial infarction (21%), stroke (15%), cancer (21%), infection (10%), renal failure (4%), respiratory disease (2%), and the rest 27% from other causes (eg, accidents, etc). A strongly significant trend was observed between baseline age of the participants and all-cause mortality ($P$ for trend $< .001$). In particular, men who were older than 80 years at baseline examination had about 2 times higher risk of death when compared to those aged between 65 and 80 years (2.07, 95% CI: 1.04-4.12), whereas women who were older than 80 years at baseline examination had about 8 times higher risk of death as compared with those aged between 65 and 80 years (8.27, 95% CI, 3.00-22.77). The probability of surviving after the age of 80 years increased, whereas the aforementioned probability showed a progressive reduction as far as the middle of the eighth decade of life (Figure 1).

Moreover, 120 (72 men, 22.6%, $P$ for gender comparisons $=$ .006) of the participants (ie, 1830 cases per 10 000 inhabitants) had a nonfatal event (ie, acute myocardial infarction, heart failure, stroke, cancer, and pulmonary infection, other infection, renal failure, and accidents) during the follow-up period. The 4-year incidence of CVD was 420 cases per 10 000 inhabitants; particularly, the CVD incidence was 520 cases per 10 000 inhabitants and 320 cases per 10 000 women ($P$ for gender difference $= .20$). In Figure 2, the survival curves for all-cause mortality as well as CVD nonfatal events are presented separately in men and women.

**Table 1.** Characteristics of the Ikaria Study's Participants at Baseline Examination in Year 2009.[a]

| | Men (n = 330) | Women (N = 343) | P |
|---|---|---|---|
| Age, years | 75 ± 7 | 76 ± 6 | .72 |
| History of hypertension, % | 69 | 75 | .08 |
| Systolic blood pressure, mm Hg | 144 ± 19 | 143 ± 20 | .34 |
| Diastolic blood pressure, mm Hg | 80 ± 11 | 79 ± 12 | .14 |
| History of hypercholesterolemia, % | 62 | 69 | .08 |
| Total cholesterol levels, mg/dL | 192 ± 42 | 203 ± 39 | .001 |
| Triglycerides, mg/dL | 147 ± 87 | 133 ± 56.2 | .01 |
| HDL-C, mg/dL | 44 ± 10 | 49.7 ± 11 | .001 |
| LDL-C, mg/dL | 121 ± 33.4 | 127 ± 33 | .01 |
| History of diabetes mellitus, % | 32 | 25 | .05 |
| Glucose levels, mg/dL | 110 ± 33 | 106 ± 34 | .11 |
| History of cardiovascular disease, % | 23 | 19 | .17 |
| Metabolic syndrome, % | 52 | 63 | .007 |
| Waist circumference, cm | 105 ± 11 | 102 ± 13 | .007 |
| Obesity, % | 29 | 30 | .72 |
| Body mass index, kg/m$^2$ | 28.0 ± 4.0 | 28.5 ± 5 | .14 |
| Creatinine clearance, mL | 72 ± 22 | 65 ± 20.6 | .001 |
| GDS score (0-15) | 3.2 ± 3 | 4.8 ± 3.5 | .001 |
| Current smokers, % | 23 | 11 | .001 |
| Education level, years of school | 8.6 ± 3.6 | 7.3 ± 3 | .001 |
| Physical inactivity, % | 12 | 20 | .007 |
| MedDietScore (0-55) | 37.9 ± 2.8 | 38 ± 3.6 | .77 |

Abbreviations: GDS: Geriatric Depression Scale; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Data are presented as mean ± standard deviation and relative frequencies. Comparisons between gender groups for the continuous variables were performed using the *t* test or the Mann-Whitney *U* test for the skewed variables (triglycerides, creatinine clearance, and glucose) and for the categorical variables using the $\chi^2$ test.

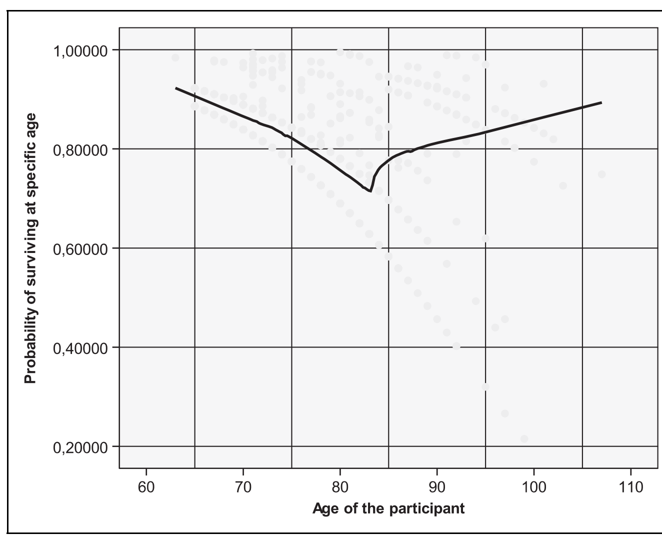


**Figure 1.** Probability of surviving at specific age of the older adults participated in the Ikaria study.

Regarding the association between age of the participants at baseline evaluation and the development of CVD, no significant relationship was observed, in both men and women. In Tables 2 and 3, the predictors of all-cause mortality and CVD

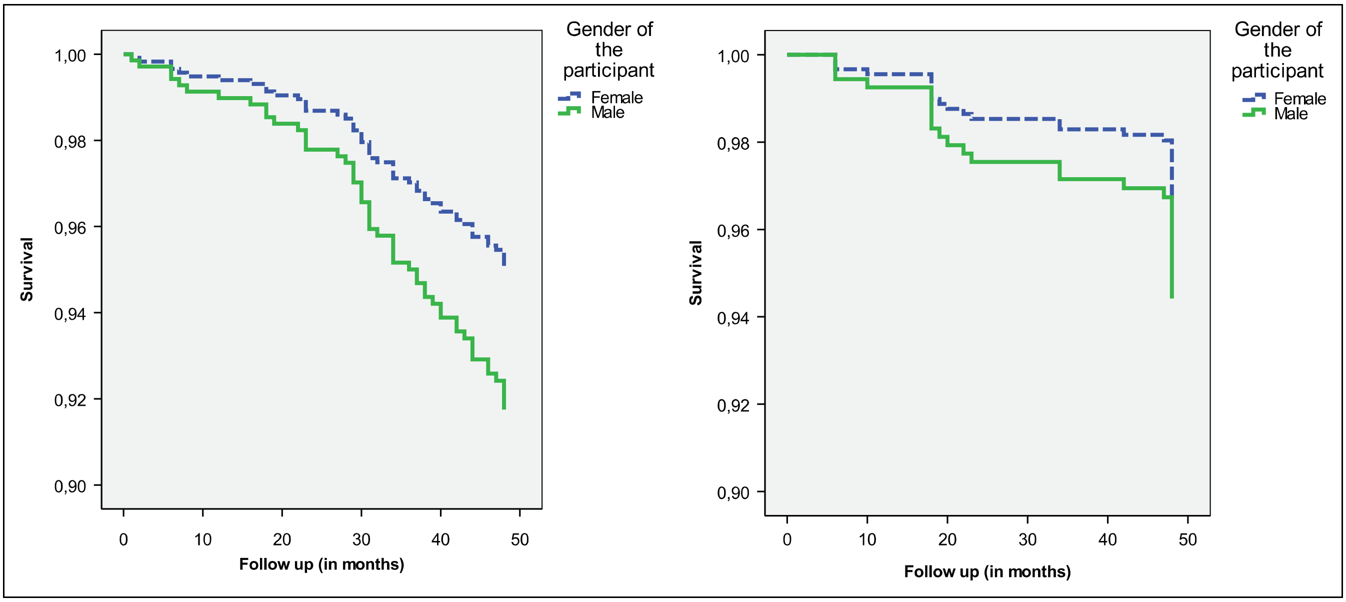


**Figure 2.** Cumulative survival curves for all-cause mortality (left) and CVD incidence (right) during the 4-year period (2009 to 2013).

**Table 2.** Predictors of 4-year All-Cause Mortality as a Function of Baseline Risk Factor Levels Among Men (n = 330) and Women (n = 343) Participants Older Than 65 years at Baseline Examination: the Ikaria Study.

| | Hazard Ratio | 95% Confidence Interval | | *P* |
|---|---|---|---|---|
| Age at entry (per 1 year) | 1.098 | 1.031 | 1.168 | .003 |
| Men vs women | 2.850 | 1.075 | 7.554 | .035 |
| Body mass index (per 1 kg/m$^2$) | 1.023 | 0.910 | 1.151 | .702 |
| History of diabetes (yes vs no) | 1.054 | 0.397 | 2.801 | .916 |
| History of hypertension (yes vs no) | 0.969 | 0.328 | 2.861 | .955 |
| History of hypercholesterolemia (yes vs no) | 1.268 | 0.496 | 3.241 | .620 |
| Pulse pressure (per 1 mm Hg) | 0.997 | 0.968 | 1.026 | .817 |
| Heart rate (per 1 beats per minute) | 1.024 | 1.000 | 1.049 | .048 |
| Physical activity (yes vs no) | 0.620 | 0.195 | 1.970 | .418 |
| Smoking status (yes vs no) | 1.584 | 0.544 | 4.608 | .399 |
| Urea (per 1 mg/dL) | 1.023 | 1.007 | 1.040 | .006 |
| History of cardiovascular disease (yes vs no) | 1.948 | 0.711 | 5.335 | .195 |

incidence are presented, respectively. Due to the small number of deaths, no cause-specific analysis was performed, and for the same reason, CVD outcome included both fatal and nonfatal events. Beyond the classical risk factors included in the models presented in the tables, that is, age, gender, smoking, physical activity status, history of CVD, and other comorbidities, pulse pressure (ie, the difference between systolic and diastolic blood pressure) was entered as a proxy of aortic distensibility and urea was included as a marker of renal function. Level of adherence to the Mediterranean diet using the MedDietScore, education status in years of school, and depression level through the GDS score were also included in the models but were insignificantly associated with the outcomes (all *P*s > .30) and removed from the final models presented here due to the violation of the assumption of proportionality. Among the investigated characteristics, increased age, male gender, high heart rate as well as urea levels were significant predictors of overall mortality (Table 2). When waist circumference or waist to hip ratio was entered in the model in the place of body mass index (BMI), no significant associations were observed (all *P*s > .20). Depression status was borderline but positively associated with all-cause mortality (HR per 1/15 increase in the GDS scale = 1.09; 95% CI, 0.98-1.19), after the aforementioned adjustments were made. In contrast, cognitive impairment was not associated with the participants' mortality rate (*P* = .89).

Although the overall quality of diet, that is, MedDietScore, was not associated with all-cause mortality, energy intake was inversely associated with mortality (HR per 100 kcal, 0.92; 95% CI, 0.86-1.00), after adjusting for the covariates included in the model presented in Table 1. Moreover, olive oil intake was favorably associated with a lower risk of death (0.92 for daily use in cooking and meals vs no regular use; 95% CI, 0.95-0.98), after adjusting for the aforementioned covariates. None of the food groups or macronutrients intake was associated with the outcome (all *P* > .20).

Moreover, red blood cells distribution width (1.077 per unit, 95% CI: 1.006-1.15, *P* = .03), left ventricular mass index (1.01 per unit, 95% CI: 1.001-1.02, *P* = .03), maximum left atrial volume (1.02 per unit, 95% CI: 1.009-1.03, *P* = .002), left ventricular ejection fraction (0.94 per unit, 95% CI: 0.89-0.98, *P* = .01), and depression (1.07 per 1/15 increase in the GDS scale, 95% CI: 0.99-1.17) were also associated with all-cause mortality, after adjusting for age, sex, physical activity, arterial hypertension, obesity, current smoking, diabetes mellitus, and hypercholesterolemia. Additionally, a trend was found between thyroid-stimulating hormone (TSH) and all-cause mortality

**Table 3.** Predictors of 4-year CVD Events (Fatal or Nonfatal) as a Function of Baseline Risk Factor Levels Among Men (n = 330) and Women (n = 343) Participants Older Than 65 years at Baseline Examination: the Ikaria Study.

| | Hazard Ratio | 95% Confidence Interval | | *P* |
|---|---|---|---|---|
| Age at entry (per 1 year) | 1.029 | 0.944 | 1.121 | .515 |
| Men vs women | 0.693 | 0.200 | 2.405 | .564 |
| Body mass index (per 1 kg/m$^2$) | 0.920 | 0.780 | 1.085 | .320 |
| History of diabetes (yes vs no) | 1.733 | 0.524 | 5.735 | .368 |
| History of hypertension (yes vs no) | 0.493 | 0.139 | 1.751 | .274 |
| History of hypercholesterolemia (yes vs no) | 0.552 | 0.173 | 1.767 | .317 |
| Pulse pressure (per 1 mm Hg) | 1.041 | 1.007 | 1.076 | .019 |
| Heart rate (per 1 beats per minute) | 1.010 | 0.973 | 1.048 | .596 |
| Physical activity (yes vs no) | 1.214 | 0.301 | 4.905 | .785 |
| Smoking status (yes vs no) | 1.008 | 0.980 | 1.037 | .594 |
| Urea (per 1 mg/dL) | 2.398 | 0.557 | 10.336 | .241 |
| History of cardiovascular disease (yes vs no) | 1.722 | 0.618 | 4.800 | .299 |

(1.04 per unit, 95% CI: 0.99-1.11, $P = .10$), after the same adjustments were made.

Focusing the analysis on CVD fatal or nonfatal events, it was revealed that pulse pressure levels at baseline examination were significantly and positively associated with the outcome (Table 3). None of the food groups or macronutrients intake was associated with the outcome (all *P*s > .20). Depression status was also borderline but positively associated with CVD event risk (1.12 per 1/15 increase in the GDS scale, 95% CI: 0.98-1.28), after the aforementioned adjustments were made, whereas cognitive impairment was not associated with the participants' CVD risk ($P = .25$). Moreover, thyroid TSH (1.05 per unit, 95% CI: 1.006-1.11, $P = .02$), left atrial maximum volume (0.99 per unit, 95% CI: 0.99-1.00, $P = .11$), coffee (0.99 per 240 mL/day, 95% CI: 0.99-1.00, $P = .11$) and tea drinking (0.99 per 240 mL/day, 95% CI: 0.98-0.99), fruit intake (0.99 per 1 portion/day, 95% CI: 0.99-0.99), and serum insulin (0.91 per unit, 95% CI: 0.81, 1.00, $p = .10$) were also associated with CVD mortality, after adjusting for age, sex, obesity, arterial hypertension, diabetes mellitus, hypercholesterolemia, physical activity, current smoking, and CVD history. None of the other characteristics studied in this work were significantly associated with the mortality rate or CVD risk of the participants.

The majority of the participants (ie, 9 of the 10) had excellent mental status according to the clinical evaluation took place by the study's investigators using the MMSE scale. Moreover, more than 95% of the participants reported that they do have close friends, they do not feel abandoned and socially isolated, and they usually meet their relatives, friends, and neighbors, in, almost, a daily basis. No significant changes were observed regarding depression status of the participants, as measured using the GDS score, during the 4-year follow-up ($P = .15$). Seventy-eight percent of the participants reported engaged in various types of daily physical activities (ie, fishing, walking, gardening, etc). Most of the participants (ie, 65%) reported that they consume a nutritional pattern close to the Mediterranean diet, that is, rich in fruits, vegetables, legumes, fish instead of red meat, they consume olive oil on a daily basis, and they drink 1 or 2 glasses of wine daily. The 4-year incidence of hypertension was 900 new cases of the 10 000 inhabitants, the 4-year incidence of hypercholesterolemia was 650 new cases of the 10 000 inhabitants, and the 4-year incidence of diabetes was 690 new cases of the 10 000 inhabitants. No gender-specific differences were observed. Only 8% of the participants reported that the current financial crisis affected their adherence to medical treatment. Seventy-seven percent of the participants reported that they have at least moderate perspective of their quality of life, whereas 18% of the participants reported excellent health quality.

## Discussion

In the last decades in the developed world, life expectancy has increased due to the achievements in medical treatment and the improvement in social–economical status of the population.[11-13] This also creates a dramatic fall in the ratio of workers to seniors that causes major impacts on the solvency of social security and health care systems. Thus, the research of factors related not only to mortality but also to morbidity and especially CVD, which remains the first cause of hospitalization, attracts the interest of nowadays medicine.[14] In this work, the 4-year survival rate, the causes of mortality, and morbidity were measured, whereas clinical, anthropometric, and lifestyle characteristics were evaluated in respect to overall and cardiovascular mortality in a cohort of older inhabitants of Ikaria Island. This study illustrated that among individuals with a mean age of 75 years, age, male gender, blood urea measurement, increased heart rate, decreased left ventricular performance, thyroid abnormalities, and pulse pressure were the most significant clinical predictors for mortality. Among lifestyle habits, nutritional aspects of daily olive oil consumption and moderate coffee intake were also associated with increased survival.

Previous scientific work in Greek area, from the Seven Countries study, had revealed that in middle-aged men, age, diastolic blood pressure, smoking habits, physical activity, forced expiratory volume, and skinfold thickness were significantly associated with all-cause mortality, whereas BMI was significantly related to CHD mortality, during the extended period of 40 years of follow-up.[15] It is interesting to mention that in the survival models for older population, classic risk factors for cardiovascular morbidity and mortality are missing.

Among emerging risk factors, the role of diet on specific age-related diseases has been studied extensively, but few investigations have adopted a more holistic approach to determine its association with overall health at older ages. The Seven Countries Study characterized diets in countries with high CHD rates (eg, northern Finland) and those with low CHD rates (eg, Crete) and attributed much of the observed longevity in South Europe and Japan on their dietary habits.[1,16,17] In this study, during the 4-year follow-up, the overall diet pattern was not significantly important for mortality, although olive oil as a major component of Mediterranean diet showed beneficial effect on overall survival. Those beneficial effects have been attributed to the known anti-inflammatory and antioxidant effects of monounsaturated fatty acids, phenolic compounds, and Vitamin E, found in olives.[18-20] Another long-term nutritional and lifestyle habit that was observed to be related with decreased mortality is regular moderate coffee consumption. Especially, the boiled Greek type of coffee, which is traditionally consumed, has shown to have cardioprotective properties due to the presence of chlorogenic acid, which is a polyphenol, whose metabolites, caffeic and ferulic acids, have anti-inflammatory effects. Moreover, other micronutrients, such as flavonoids, magnesium, potassium, niacin, and vitamin E, contribute to the observed health effects of coffee consumption, mainly because of their antioxidant properties.[21-23] In the National Institutes of Health-AARP Diet and Health Study that examined 2 29 119 men and 1 73 141 women, coffee consumption after adjustment for tobacco smoking status and other potential confounders was significantly inversely associated with total mortality.[24]

During aging, dynamic and incremental alterations take place in structure and function of the cardiovascular system. These alterations concern the cellular and extracellular composition of myocardial tissue, cardiomyocyte hypertrophy, apoptosis, and regeneration. Increased left ventricular mass has been related to advanced age and accumulation of cardiovascular risk factors, deteriorating diastolic function, increasing left ventricular relaxation time, and left atrial volume and pressure. Those alterations act as prognostic factors for all-cause morbidity in the individuals of the Ikaria study. In this topic, the Framingham Heart Study revealed that alterations in cardiac morphology during aging are associated with the accumulation of cardiovascular risk factors and metabolic abnormalities.[25] Additionally, aging causes progressive stiffness, dilatation, and lengthening of the arteries; thus low arterial distensibility, leading to hypoperfusion of several organs, penetration of small cerebral vessels, and augmentation of vascular resistance has long been recognized as an indicator of atherosclerosis and future cardiovascular events.[26,27,28] Pulse pressure, which reflects a simple noninvasive approach for the evaluation of aortic dilatation, represents the increase in cardiac afterload due to an augmented systemic resistance.[27,28] The mechanical behavior of the aortic wall is complex, and it is determined by several factors, including sympathetic stimulation.[29,30] Heart rate variability provides an accurate view of the influence of autonomic nervous system on heart activity, whereas low heart rate variability has been related to increased cardiovascular morbidity and mortality.[31,32] In the Ikaria study, each increase in rest heart rate by 10 beats per minute was related to all-cause mortality. Increased heart rate may represent the physical status of the individuals or even the presence of chronic pathological conditions or poor health status. The correlation between heart rate and maximum life span seems to be due to both basal metabolic rate and cardiovascular-related mortality risk. In that perspective, alterations in heart rate variability, which reflect autonomic system balance, may influence aortic elastic properties beyond the effect of aging in arterial system. Thus, older individuals in this study with increased pulse pressure (PP) values and higher rest heart rate had more pronounced cardiovascular mortality during the follow-up period.

Among renal function indices, urea values have prognostic value in the course of chronic diseases, as they correlate with neurohormonal activation and hemodynamic alterations, related to renal hypoperfusion. In older individuals, aortic stiffness and reduced cardiac output deteriorate renal function, which in turn predict overall morbidity and mortality.[33] Additionally, red blood cell distribution showed a positive relationship with overall mortality, in line with the results of previous studies, as it represents an indicator of chronic inflammation related to the course of several diseases.[34]

Aging can be defined as a decline in performance and fitness, creating difficulty in adapting to new situations. The main purpose of gerontology is achieving successful aging, which means good mental health, maintenance of social life, preserved functional capacity, and lack of depression. The majority of participants in the Ikaria study presented excellent mental status according to the clinical evaluation, with no significant changes observed during the 4-years of follow-up. However, a great percentage of them reported lack of social support, although the vast majority expressed having satisfactory perspective of their quality of life. Most of them reported engaged in various types of daily physical activities (ie, fishing, walking, gardening, etc) and consuming a nutritional pattern close to the Mediterranean diet, that is, rich in fruits, vegetables, legumes, olive oil, and moderate alcohol consumption. Those lifestyle habits have also been described in other high longevity communities nowadays, but Hippocrates (400 BC) had first referred to behaviors promoting healthy aging: “All parts of the body which have a function if used in moderation and exercised in labors in which each is accustomed, become thereby healthy, well developed and age more slowly; but if unused and left idle they become liable to disease, defective in growth and age quickly.”[35]

### *Limitations*

Because of the observational design of the study, the results should be interpreted and generalized with conscious. The physical activity assessment tool used here has not been validated for older adults. The MMSE score could be biased by the interview setting and the way performed, although an effort was given to apply the same procedures for all participants.

## Conclusion

Based on 4 years of observation in older individuals in Ikaria Island, age, depression, left ventricular hypertrophy, volume of left atrial, left ventricular ejection fraction, red blood cell distribution, olive oil consumption, and TSH were statistically significant predictors for all-cause death. Also, age, male gender, heart rate, serum urea levels, pulse pressure, plasma insulin levels, left atrial volume, and coffee consumption were found significant predictors for CVD mortality. Moreover, the long-term adoption of a nutritional pattern close to the Mediterranean diet, the presence of physical activity, and the optimistic behavior seem to characterize the very old men and women who were alive at the 4-year follow-up. Although in this cohort of older participants a lack of established risk factors for CVD mortality was noticed, it is hard to claim that our findings suggest causal evidence for determinants of longevity, as longer follow-up should be completed.

## Authors' Note

The Ikaria Study Group included Vasiliki Metaxa, MD, Marina Zaromytidou, MD, Erifili Venieri, MD, Savvas Mazaris, MD, Maria Kariori, MD, Kalliopi Katte, MD, and Kostas Zisimos, MD.

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## Declaration of Conflicting Interests

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