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Anti-Inflammatory Nutrition and Successful Ageing in Elderly Individuals: The Multinational MEDIS Study

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Keywords
Successful ageing · Dietary habits · Inflammation · Older adults · Mediterranean basin

Abstract
Background: The role of diet and inflammation in successful ageing is not transparent, and as such, is still being investigated. The aim of the present work was to evaluate the inflammatory potential of dietary habits in the successful ageing of a random sample of older adults living in the Mediterranean basin and who participated in the MEDIS (MEDiterranean ISlands) study. ***Methods:*** During 2005–2016, 3,128 older adults (aged 65–100 years) from 24 Mediterranean islands and the rural Mani region (Peloponnesus) of Greece were enrolled in the study. A multidimensional successful ageing index consisting of 10 components was employed. A validated and reproducible Food Frequency Questionnaire (FFQ) was used to evaluate the dietary habits of the older adults. A nutrition anti-inflammatory (NAI) score based on the participants' specific dietary habits was assessed. ***Results:*** Participants with high NAI scores (proinflammatory nutrition) had a higher prevalence of hypercholesterolemia and lower levels of successful ageing. After adjusting for several confounders, the NAI score was associated with successful ageing (–0.03, 95% CI –0.5 to –0.006). Stratified analysis by gender and advanced age revealed heterogeneity in the NAI score, predicting successful ageing. ***Conclusions:*** The in-

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flammatory potential of nutrition was reported as an important factor for successful ageing, suggesting that further research is needed on the role of anti- and proinflammatory dietary habits in healthy and successful ageing.

Introduction

Ageing remains one of the major public health challenges globally [1]. It was estimated that in 2015, the population over 65 years of age approached 1.5 billion [2]. In order to reduce the negative impact of ageing, great efforts are being put in to achieve healthy ageing. Healthy and successful ageing is considered as a low probability for disease and disability, high cognitive and physical capacity, as well as active participation in various social activities [3, 4]. The aforementioned state of "successful ageing" is related to lower mortality rates [5] and better health outcomes [6]. The process of "healthy," "active," and "successful" ageing itself is quite complex and is associated with a variety of factors. Based on the aforementioned, the MEDIS (MEDiterranean ISlands) investigators have created a successful ageing index (SAI) using 10 specific attributes. The MEDIS SAI was reported to be multidimensional with the 3 following components: psychosocial-economic, bioclinical, and lifestyle [6].

The determinants of successful ageing and, specifically, the role of the diet's inflammatory potential in ageing remain poorly understood. Previously, well-documented studies have reported a strong association between nutrition and inflammatory marker regulation [7–9]. The Mediterranean diet as a healthy dietary pattern [9], as well as flavonoids, polyphenols, n-3 fatty acids and other food components (i.e., coffee, tea, wine, etc.) are well known for offering anti-inflammatory protection [10]. Moreover, it has been reported that the process of inflammation, oxidative stress, and advancing age is strongly related to biological pathways that interact with the dietary habits of older adults [11]. Recently, Tyrovolas et al. [12] reported that increased energy intake and a positive energy balance are associated with lower successful ageing levels. Although it is widely accepted that inflammation throughout atherosclerosis and endothelial dysfunction pathways [13] is associated with cardiovascular health and healthy ageing [14], there is a lack of evidence on the inflammatory role of the diet or specific food items in the ageing process.

Given the complexity of the successful ageing pathway and its interrelation with inflammation and oxidative stress, together with the lack of data among Mediterranean older populations, the aim of the present work was to evaluate the association between the inflammatory potential of nutrition and successful ageing in a random sample of older adults living in the Mediterranean basin and who participated in the MEDIS study.

Methods

The MEDIS Study Sample

Between 2005 and 2016, a population-based, multinational, convenience sampling was performed to voluntarily enroll older people from 24 Mediterranean islands from Greece, Republic of Cyprus, Malta, Italy, and Spain [6]. 49.9% of the study participants were males. According to the study protocol, individuals were not eligible for inclusion if they resided in assisted-living centers, had a clinical history of cardiovascular disease (CVD) or cancer, or had lived away from the island for a considerable period of time during their lives (i.e., >5 years). These exclusion criteria were applied because the study aimed to assess lifestyle habits that were not subject to modifications due to existing chronic health conditions or by environmental factors, other than living milieu. A group of health scientists (physicians, dietitians, and nurses) with experience in field investigation collected all the required information using a quantitative questionnaire and standard procedures.

The study followed the ethical considerations provided by the World Medical Association (52nd WMA General Assembly, Edinburgh, UK, October 2000). The Institutional Ethics Board of Harokopio University approved the design and procedures of the study (reference No. 16/19-12-2006). Participants were informed about the aims and procedures of the study and gave their consent prior to being interviewed.

Evaluation of Clinical Characteristics

All the measurements taken in the different study centers were standardized, and the questionnaires were translated in all the cohorts' languages following the World Health Organization translation guidelines for tool assessment [15]. Weight, height, and waist circumference were measured using a standard protocol; body mass index (BMI) was calculated as the ratio of weight by height squared (kg/m^2). Overweight was defined as BMI 25–29.9, and obesity was defined as BMI >29.9. Diabetes mellitus (type 2) was determined by fasting plasma glucose tests and was analyzed in accordance with the American Diabetes Association diagnostic criteria (glycated hemoglobin A1c ≥6.5 or fasting blood glucose levels >125 mg/dl or 2-h plasma glucose >200 mg/dl during an oral glucose tolerance test or a random plasma glucose >200 mg/dl, or by a prior diagnosis of diabetes). Participants who had blood pressure levels ≥140/90 mm Hg or used antihypertensive medications were classified as hypertensive. Fasting blood lipid levels (HDL, LDL cholesterol, and triglycerides) were also recorded, and hypercholesterolemia was defined as total serum cholesterol levels >200 mg/dL or the use of lipid-lowering agents according to the NCEP ATPIII guidelines [16]. Symptoms of depression during the previous month were assessed using the validated Greek version (also translated in all the cohort's languages) of the shortened, self-report Geriatric Depression Scale (GDS) (range 0–20) [17]. Participants

with a GDS score >11 were included in the severe depressive symptoms group, while those with a GDS <10 were included in the mild and low depressive symptoms group.

Evaluation of Dietary Habits, Sociodemographic, and Other Lifestyle Characteristics of the Participants

Dietary habits were assessed through a semiquantitative, validated, and reproducible food frequency questionnaire [18]. The frequency of consumption of various food types and beverages (i.e., meat and meat products, fish and seafood, milk and other dairy products, fruits, vegetables, greens and salads, legumes, cereals, coffee, and tea and soft-drinks) on a daily, weekly or monthly basis, was assessed. Furthermore, intake of various alcoholic beverages (i.e., wine, beer, etc.) was measured in terms of wine glasses adjusted for ethanol intake (e.g., one 100 ml glass of wine was considered to have 12% ethanol). Also, the consumption of various types of coffee drinks (i.e., boiled, filtered, espresso, and instant) as well as tea consumption (i.e., green, black) was measured in terms of general consumption per day and as well as cups per day. Energy and macronutrient intake was evaluated through the quantification of the portions of foods and beverages consumed, using food composition tables [19, 20].

The calculation of a nutrition anti-inflammatory (NAI) score for the MEDIS study sample was based on the previous literature [21, 22]. Based on the validated MEDIS Food Frequency Questionnaire (FFQ), a total of 7 food components were used for the development of a nutrition-related inflammatory score. These were: energy balance, proteins, carbohydrates, total fat as percent of energy intake, tea, coffee, and alcohol consumption. The nutrition-related inflammatory score was created in order to avoid the collinearity phenomenon between the aforementioned components that is essential for correctly performing a multivariable statistical analysis [23]. Individual ratings (–1 and 1) in each of the 7 components were assigned, according to their high anti-inflammatory or low anti-inflammatory effect, respectively [24, 25]. Higher NAI scores imply lower anti-inflammatory nutrition, following a similar coding methodology that has been reported in the literature [21]. If energy balance was >0 then a score of 1 was given, and if it was <0, a score of –1 was given. If protein, carbohydrates, and total fat consumption were within the recommended intakes [26], a score of –1 was coded, while if it was over or lower than the recommended intake, the score was 1. Tea, coffee, and alcohol consumption were coded as –1, while no consumption was coded as 1. Moreover, the tertiles of the NAI score were computed in order to classify nutrition as high, medium, and low anti-inflammatory.

Sociodemographic characteristics, such as age, gender, years of school, financial status, and lifestyle characteristics, such as smoking habit and physical activity status, were recorded. Regarding financial status, the participants were asked to report their mean income during the previous 3 years using a 4-point scale (low, inadequate to cover daily expenses = 1, medium, trying hard to cover daily expenses = 2, good, adequate to cover daily expenses = 3, very good, very adequate to cover daily expenses = 4); this scale was decided upon because of the variety of the populations studied, as well as the common difficulty of accessing exact financial data. The participants that were in the upper category were classified as participants with a high financial status, while all the others were classified as low and medium financial status (high vs. low-medium financial status). Current smokers were defined as smokers at the time of the interview. Former smokers were defined as those who had previously smoked, but had not done so for a year or more. The remaining participants were defined as occasional or non-current smokers. Physical activity was evaluated in MET minutes per week, using the shortened and validated in Greek version of the self-reported International Physical Activity Questionnaire (IPAQ) [27] which was translated into all the languages used in the cohort. Minimally active or "health-enhancing physical activity active" were classified as individuals who reported at least 3 MET minutes per week. Furthermore, the weekly frequency of physical activity was recorded. Additionally, in order to evaluate social participation, the weekly frequency of their social activities with their family, their friends as well as their yearly frequency of excursions were recorded.

Further details about the MEDIS study protocol may be found elsewhere [28].

Evaluated Outcomes

Following the multidimensional approach to successful ageing that has already been reported by the MEDIS study group [6], 10 components (i.e., education, financial status, physical activity, BMI, GDS score, participation in social activities with friends, with family, yearly excursions, CVD risk factors score, and MedDietScore) were incorporated for the measurement of successful ageing. The SAI was represented as the cumulative score of the 10 components (theoretical range 0–10); specifically, individual ratings (from 0 to 1) in each of the 10 components were assigned, according to their positive or negative (i.e., reverse scoring) influence on successful ageing.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequencies. Comparisons of continuous variables between groups were performed using the independent samples *t* test (for normal distribution) and the Mann-Whitney U test (for skewed distribution). Associations between categorical variables were tested using the χ^2 test. Linear regression models were applied in order to evaluate the association between various sociodemographic, bioclinical, and nutritional factors (independent variables) and the level of successful ageing (dependent outcome). Collinearity was tested using the variance inflation factor criterion (values >4 suggested collinearity between independent variables, and one of them was excluded from the model). The assumption of homoscedasticity was tested by plotting the scatter plot of standardized residuals over the predicted score values. Results from linear regression models are presented as *b* coefficients and their 95% confidence Intervals. All reported *p* values were based on two-sided tests. The SPSS software (version 20) was used for all calculations (IBM Statistics, Greece).

Results

The total range of the NAI score of the MEDIS sample was –7.0 to +5.0. In the entire sample, the mean NAI score was –1.2 ± 2.3. Demographic, behavioral, clinical, and lifestyle characteristics of the total sample, categorized by NAI score tertiles, are summarized in Table 1. Compared to the 1st tertile (high anti-inflammatory nutrition), the

Table 1. Demographic, behavioral, clinical, and lifestyle characteristics of the multinational MEDIS sample, nutrition anti-inflammatory (NAI) score categorization

	NAI score			p^a
	1st tertile	2nd tertile	3rd tertile	
Total subjects, *n*	1,056	770	713	
Age, years	74.4±7.3	73.5.1±7.5	73.7±8.1	0.03
Male sex	55	53	38	0.001
Urban residence, %	64	63	53	<0.001
Obesity, %	32	31	33	0.86
Education, years of school	6.8±3.9	6.9±3.9	6.4±4.1	0.11
High financial status, %	20	19	18	0.79
Living alone, %	23	29	27	0.02
Current smoking, %	17	17	12	0.03
Physical activity, %	52	38	34	<0.001
Hypertension, %	63	62	64	0.75
Diabetes mellitus, %	20	23	25	0.09
Hypercholesterolemia, %	45	52	51	0.007
Successful ageing (0–10)	2.7±1.3	2.6±1.2	2.3±1.3	<0.001

[a] Comparisons of continuous variables between groups were performed using the independent samples *t* test (for normal distribution) and the Mann-Whitney U test (for skewed distribution).

participants in the 2nd and the 3rd tertile (medium and low anti-inflammatory nutrition) were females (p = 0.001), less urban residents ($p < 0.001$), less physically active ($p < 0.001$), less smokers ($p = 0.03$), and they had a higher prevalence of hypercholesterolemia ($p = 0.007$) and lower level of successful ageing ($p < 0.001$). Moreover, no differences in obesity, education level, financial status, diabetes mellitus, and hypertension were observed between the NAI score groups.

As shown in Table 2, after adjusting for age, gender, urban residence, waist circumference, and smoking habit, a consistent relationship between NAI score and the level of successful ageing (model 1 to model 3) was found. Specifically, it was found that an increase in NAI score (low anti-inflammatory nutrition) was associated with lower levels of successful ageing (*b* coefficient: –0.03, 95% CI –0.5 to –0.006, $p = 0.014$).

Then, the interactions between NAI and gender and age group were tested (Table 2). Although no significant interaction with gender and NAI was observed (p for interaction = 0.28), the analysis was split by sex, considering the fact of gender paradox in exploring healthy ageing [6]. The analysis revealed that in females, a low anti-inflammatory nutrition was inversely associated with the successful ageing score (–0.03, 95% CI –0.64 to –0.003, p = 0.003); however, in males, there was no association between the NAI score and the level of successful ageing ($p = 0.27$).

A significant interaction was observed between age and NAI (p for interaction = 0.02). Thus, age group analysis showed that the lower the anti-inflammatory dietary habits of an older individual, the lower the level of successful ageing. This association was significant in the group of octogenarians (–0.05, 95% CI –0.09 to –0.001, $p = 0.04$), but not in the rest of the participants (–0.02, 95% CI –0.05 to 0.006, $p = 0.13$).

Finally, the association between anti-inflammatory nutrition and healthcare services use was also tested. After adjusting for various confounders such age, sex, etc., no relation between NAI score and annual health care services was found ($p = 0.76$).

Discussion

The present work revealed an inverse association between low anti-inflammatory nutrition, and successful ageing; in particular, the multiadjusted analysis revealed that the consumption of a low anti-inflammatory diet was associated with lower levels of successful ageing, irrespective of age, gender, residence area, smoking habit and waist circumference. In addition, when the analysis was stratified by gender and age group, this association remained significant only for females and in those over 80 years old. These relationships have rarely been studied globally; moreover, it is the first time that an association

Table 2. Results from linear regression (*b* coefficient, 95% CI) performed to evaluate the relationship between various sociodemographic, bioclinical, and lifestyle characteristics and nutrition anti-inflammatory (NAI) score in association with the level of successful ageing (n = 1,701)

	Model 1		Model 2		Model 3			
	b	95% CI	*b*	95% CI	*b*	95% CI		
Overall								
NAI score (per 1)	–0.05	–0.7, –0.2	–0.03	–0.5, –0.004	–0.03	–0.5, –0.006		
Age (per 1 year)	–	–	–0.02	–0.025, –0.01	–0.01	–0.02, –0.009		
Sex (males vs. females)	–	–	0.58	0.48, 0.68	0.45	0.32, 0.57		
Urban residence (yes vs. no)	–	–	–0.02	–0.12, 0.08	–0.10	–0.22, 0.13		
Waist circumference (per 1 cm)	–	–	–	–	–0.29	–0.03, –0.02		
Current smoking habit (yes vs. no)	–	–	–	–	0.18	0.001, 0.37		
	Females		Males		65–80 years		80 years+	
	b	95% CI	*b*	95% CI	*b*	95% CI	*b*	95% CI
Subgroup analysis								
NAI score (per 1)	–0.03	–0.06,–0.003	–0.02	–0.06, 0.017	–0.02	–0.05, 0.006	–0.05	–0.09, –0.001
Age (per 1 year)	–0.01	–0.02, –0.003	–0.02	–0.03, –0.009	–	–	–	–
Sex (males vs. females)	–	–	–	–	0.48	0.34, 0.63	0.27	0.03, 0.51
Urban residence (yes vs. no)	–0.005	–0.16, 0.15	–0.23	–0.12, –0.06	–0.07	–0.20, 0.07	–0.16	–0.39, 0.08
Waist circumference (per 1 cm)	–0.03	–0.03, –0.02	–0.03	–0.04, –0.02	–0.03	–0.4, –0.02	–0.024	–0.03, –0.016
Current smoking habit (yes vs. no)	0.6	0.23, 0.96	0.04	–0.17, 0.26	0.27	0.07, 0.47	–0.19	–0.72, 0.33

of this kind has been reported among older adults of the Mediterranean basin.

Despite the lack of previous findings regarding successful ageing and nutrition-related inflammation among Mediterranean populations, a number of studies have previously reported that inflammation process is highly related to CVDs [13, 29]. Well-documented studies have reported that inflammatory markers such as interleukin-1, CRP, and others are related with CVD health [6, 30]. In support of this, our unadjusted analysis reported that the more proinflammatory dietary habits of an individual, the higher the risk for hypercholesterolemia, and there seemed to be a trend for the presence of diabetes mellitus. Previous results from the MEDIS study reported that the SAI levels of the ageing insular Mediterranean population are low, with high cardiovascular morbidity. Moreover, female gender and urban place of residence were inversely related to the MEDIS SAI [6]. In addition, the use of the SAI based only on the state of well-being has been tested in a previous paper of the MEDIS group (i.e., modified SAI was inversely associated with BMI and hypertriglyceridemia and was positively associated with tea consumption [$p < 0.001$]); however, the external validity of this modified type of successful ageing score, which focused only on the well-being, was poor (could not predict the annual use of healthcare services (*b* coefficient: 1.10, $p = 0.155$) [6].

It has been suggested that living longer is a process that reflects complex interrelations among multidimensional factors [31]. A wider picture of this concept is described throughout the successful ageing theory which has been associated with better health outcomes [3–5]. Data analysis revealed that the lower the anti-inflammatory nutrition the lower the successful ageing level among older individuals. The role of healthy diet in ageing and longevity has been well documented in the past [11, 14, 32], and well-conducted studies have shown that healthy nutrition is associated with reduced overall mortality [32]. Nutrition's inflammatory potential has been shown to be associated with various health risk factors such as CVD risk factor burden [33], glucose intolerance, dyslipidemia, components of the metabolic syndrome, as well as with anthropometric measurements and established CVD [34–36].

In addition to this, other studies have reported the relationship between dietary habits and low-grade inflammation [8, 9]. It has been illustrated that nutrition centered on meat consumption is highly related to inflammation [9, 10, 37]. In contrast, a diet centered around vegetable or fruit consumption is inversely associated with inflammatory markers [38, 39]. Moreover, it is well known that high adherence to the traditional Mediterranean dietary pattern has been associated with lower inflammation levels in the human body [40]. Previous studies on dietary habit inflammatory potential and various inflammatory surrogates (i.e., CRP, TNF-α, IL-6, homocysteine, etc.) have reported significant associations [41–43]. Inflammation, oxidative stress, and healthy ageing are strongly related pathways that are interrelated by the older individual's nutrition [11, 12]. However, the exact

relationship between ageing, healthy eating and the human body's low-grade inflammation status still remains unclear [12]. Antioxidant nutrition components (such as flavonoids, polyphenols, vitamins), as well as specific fatty acids, have been proposed among others as potential nutrition mechanisms that could beneficially contribute to the favorable level of inflammation markers [25, 44].

To further explore the association between successful ageing and nutrition's inflammatory potential, an additional multivariate analysis stratified by sex and age group was applied. This association between anti-inflammatory nutrition and successful ageing levels remained significant only for females and for octogenarians. Various well-documented global studies have reported that females live longer with higher morbidity rates compared to males. Since the role of different trajectories in healthy ageing has also been described recently, the reported result of an anti-inflammatory nutrition, could also possibly explain the different gender morbidity levels [6]. Advanced age has been related to more plasma and/or serum levels of inflammatory mediators (i.e., cytokines, acute phase proteins, etc.) and to other mediating inflammation factors, such as ageing body composition changes, sex hormones, asymptomatic infections, Alzheimer disease [44], and the applied analysis reported a significant association between holistic nutrition's inflammatory potential and successful ageing in the octogenarians. All of the above studies support the proposed relationships between successful ageing, and the NAI score in older individuals, with specific heterogeneity among different population groups. Due to the complexity of ageing, identifying possible anti-inflammatory nutrition-related determinants is of major importance to inform public health authorities and enhance public health nutrition planning.

Strengths and Limitations

The present study has several strengths. To the best of our knowledge, it is the first study that evaluated the effect of the diet's inflammatory potential in the successful ageing of a large sample of "healthy," independently living older people in the Mediterranean basin. The main limitation of the study is its cross-sectional design, and thus causal relationships cannot be inferred. Moreover, people with a history of cancer and CVD were excluded from sampling; therefore, a potential selection bias may exist. Also, the cumulative SAI that was previously developed by simply adding the presence of the common determinants of the individuals may not accurately estimate the successful ageing status. However, this methodology was based on a standard procedure described in the literature and has previously been used in other ageing-associated definitions (i.e., frailty, healthy ageing) [3, 6]. For the development of NAI, 7 semi-quantitative nutrition components were used, and thus, the application of discrete and not continuous coding was obligatory; a fact that may limit the presented results.

Conclusion

The present work revealed the anti-inflammatory role of nutrition in the level of successful ageing among older Mediterranean adults. It is of major interest to understand the role of nutrition and its inflammatory dynamic on the transforming nature of ageing. The gender and older age-related heterogeneity regarding successful ageing and nutrition's inflammatory potential should be taken into account by public health authorities in order to develop nutritional education programs and health promotion actions targeted at the needs of specific population subgroups. However, further exploration is needed in order to understand how the anti-inflammatory potential of nutrition is interrelated with the ageing pathway.

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Disclosure Statement

All authors declare that there is no conflict of interest.

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