

# Gender Differences in Adherence to Mediterranean Diet and Risk of Atrial Fibrillation.

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## Abstract:

**Background.** Adherence to the Mediterranean Diet (MedD) is associated with a reduction of overall mortality and mortality from cardiovascular diseases and cancer. In a previous study we found a relationship between intake of antioxidant vitamins with diet and risk of atrial fibrillation (AF). The present study focuses on gender differences relative to diet and antioxidant intake in patients (pts) with a first detected episode of AF.

**Methods.** A group of 400 pts, 205 men and 195 women, was investigated. A control group of 400 subjects, age and sex matched, was selected and compared. Nutritional parameters were assessed by a self-administered food frequency validated questionnaire (116 items) completed by an interviewer-administered 24 h diet recall. We previously constructed a MedD adherence score based on a prior scoring system developed for the Greek population. Consumption of cereals, vegetables, legumes, fruit, fish, dairy products, cups of espresso coffee, chocolate snacks, soda drinks and wine was investigated.

**Results.** The MedD Score was higher in women compared to men ( $28.8 \pm 2.0$  vs  $20.1 \pm 2.5$ ;  $p < 0.001$ ) and was higher in healthy subjects compared to patients with AF ( $27.9 \pm 5.6$  vs  $22.3 \pm 3.1$ ;  $p < 0.001$ ). In pts with AF the estimated intake of total antioxidants was higher in women ( $19.9 \pm 5.6$  vs  $11.2 \pm 7.4$  mmol/d;  $p < 0.001$ ), and women had higher intake of antioxidants from fruit and vegetables.

**Conclusions.** Women showed high adherence to the MedD and higher intake of antioxidants from fruit and vegetables compared to AF men. Men had higher intake of antioxidants from coffee. Women that developed AF were older, with lower adherence to the MedD, and were more sedentary.

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## Introduction:

Several epidemiologic studies have underlined the beneficial role of the Mediterranean diet in relation to all-cause mortality, coronary heart disease mortality, lipid metabolism, blood pressure levels and body mass index (1). In 1995 a score assessing adherence to the Mediterranean diet was elaborated (2) and this score, or variants of it, has been widely used to evaluate the relation of the Mediterranean diet to cardiovascular disease (3, 4).

Components of the Mediterranean diet score that act as predictors of lower mortality were moderate consumption of ethanol (mostly in the form of wine during meals), low consumption of meat and meat products and high consumption of vegetables, fruits and nuts, olive oil and legumes (5, 6).

The NHS Study found that greater adherence to a "prudent pattern", characterized by a high intake of vegetables, fruit, legumes, fish, poultry, and whole grains, was related to a lower risk of cardiovascular and total mortality in healthy women (7). The EPICOR Study found an inverse association between increased consumption of leafy vegetables and olive oil and CHD risk in a large cohort of Italian women (8).

A diet rich in fruit and vegetables and possibly low in meat products is characterized by a high intake of antioxidants, carotenoids and vitamins (i.e. C and E) that might protect against free oxygen radicals and lipid peroxidation (6,8).

Despite the numerous studies evaluating the relationship between adherence to the Mediterranean Diet and coronary artery disease, little information is available on the relationship between the Mediterranean Diet and arrhythmias (4,9). The aim of the present study was to investigate gender differences in adherence to the Mediterranean Diet in patients presenting with a first episode of atrial fibrillation (AF).

## Methods

*Patient population.* The study group included 400 patients, 205 men and 195 women of mean age  $57 \pm 10$  years presenting with first-detected AF.

Inclusion criteria were first-detected episode of AF occurring within six hours of observation. According to recent ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation, first-detected AF may be either paroxysmal or persistent AF (10). If the arrhythmia terminates spontaneously, recurrent AF is designated paroxysmal; when sustained beyond 7 days, AF is designated persistent (10). Exclusion criteria were permanent AF, any condition predisposing patients to AF, such as history of myocardial infarction, heart failure, hyperthyroidism, rheumatic heart disease, pulmonary embolism, a reduced left ventricular function, gastrointestinal tract disease, hepatic and renal disorders. We also excluded patients taking anticoagulant therapy due to dietary restriction.

The onset of AF was defined as a new and clearly recognizable onset of symptoms including palpitations, dyspnea or dizziness, or a combination of these symptoms (10). The diagnosis was confirmed by ECG. Patients were evaluated and telemetry monitoring technicians notified the investigators as soon as normal sinus rhythm was restored and electrocardiographic rhythm strips were obtained. The study protocol was approved by the Institutional Research Ethics Committee, and all subjects gave written informed consent.

Cardioversion was performed according to physician's decisions within 48 hours from the first observation of arrhythmia. Patients were subjected to saline infusion during their hospitalization while awaiting cardioversion; serum sodium, potassium, calcium and magnesium levels were assessed at baseline. Anticoagulant therapy

was started before cardioversion according to guideline (10,11).

To evaluate gender differences in adherence to the Mediterranean Diet and the effects on occurrence of AF a 1:1 case-control study was designed. Patients were compared with 400 age- and sex-matched control subjects, healthy outpatient volunteers (mean age  $54 \pm 10$  years). Control subjects were selected by general practitioners among healthy subjects following a blinded list including only sex and age. After having been informed about the general purpose and procedure of the study each subject gave written consent. All subjects lived in the same geographic area and belonged to the same ethnic group.

#### *Data Collection.*

Nutritional status was assessed by measuring weight, body mass index (BMI), waist circumference and waist-to-hip ratio (12).

The prevalence of nutritional parameters was assessed by a self-administered food frequency questionnaire (FFQ) with 116 items and completed by an interviewer-administered 7 day diet recall questionnaire on the day of hospitalization (13). The food list in the FFQ was Italianized, and foods commonly eaten in the Emilia Romagna region of Italy were added. For each food class color photographs of three different portions were displayed. Portion sizes were chosen according to many years of experience in dietary surveys in various parts of Italy (12,14). Food frequency was evaluated using three categories: daily, weekly and monthly and from 1 to 6 number of times (i.e.: once a day, 3 times a week) and was integrated with specific questions on changes in nutrition habits and lifestyle within the last year and specifically during the 7 days before the onset of symptoms.

The Mediterranean score was calculated according to Panagiotakos (3) and included 11 food groups: non-refined cereals (whole bread, pasta, rice, other grain,

etc.), fruit, vegetables, legumes, potatoes, fish, meat and meat products, poultry, full fat dairy products (butter, cream, cheese, yoghurt, milk), together with olive oil and alcohol intake. Then the frequency consumption of these foods was assessed by assigning individual ratings (from 0 to 5 or the reverse) in each of the 11 food groups cited above.

According to Panagiotakos (3), for alcohol evaluation, we assigned score 5 for consumption of less than 300 ml of alcohol/day, score 0 for consumption of more than 700 ml/day and scores 4-1 for consumption of 300, 400-500, 600 and 700 or 0 ml/day (100 ml has 12 g ethanol concentration) respectively. The score ranges from 0 to 55 (3). Higher values of this diet score indicate greater adherence to the Mediterranean diet. In the Attica Study the mean value of the Med Score was  $25.46 \pm 2.94$  in men and  $27.18 \pm 3.21$  in women and we used these values as references. (3) Food and nutrient intakes from FFQ were computed by a dietician using a database system. We also investigated the use of nutritive and non-nutritive sweetener that were included in the database.

Moreover we investigated caffeine consumption, estimated as: number of cups of coffee, type of coffee (espresso, American, decaffeinated, cappuccino), number of chocolate snacks and cola soda drinks usually consumed. We estimated caffeine intake as 1 cup of espresso coffee = 90 mg, 1 cappuccino = 110 mg, 1 cup of American coffee = 160 mg, 1 can of cola soda drink = 42 mg and one-size chocolate snack = 6 mg. (14,15).

Food and nutrient intakes from FFQ were computed by a dietician using the same database system. The nutrient database was compiled from food composition tables (12,13,14).

Antioxidant intake was evaluated by nutrient database that was supplemented with data on total antioxidant concentrations in foods.(4) The value of antioxidants was calculated as the total amount of antioxidants

derived from the combinations of individual antioxidants that occur naturally in foods. We also evaluated the percentage of antioxidants from food according to the most well known sources of antioxidants: vegetables, fruits, legumes, coffee, tea, chocolate (16).

Smoking and physical activity were also investigated. Physical activity was assessed with a self-administered questionnaire that has been shown to be valid and reliable (17).

*Statistical analysis.* SPSS, V.11.0.1 (SPSS Inc, Chicago, Ill) was used for statistical analysis. Results are presented as mean  $\pm$  SD or frequency expressed as a percentage. We compared the characteristics of patients of different genders by means of the Student *t* test for continuous variables and chi-square test for proportions. Association between variables (i.e. adherence to Med diet) in women and men was evaluated using analysis of variance (ANOVA). Association between categorical variables and adherence to Med diet groups was evaluated using the chi-square test. Univariate regression analysis was performed on the list of predictor variables using an ANOVA test. Linear regression models, using the Mediterranean Diet score as independent variable and antioxidants levels, BMI and waist circumferences as covariates, were performed to evaluate development of AF and spontaneous conversion of AF in women and in men. The results of the regression models are presented as beta-coefficient and standard error. A  $p < 0.05$  was considered statistically significant.

## Results

Clinical characteristics of patients are shown in Table 1.

In the total population the MedD Score was higher in healthy controls compared to patients that developed AF ( $27.9 \pm 5.6$  vs  $22.3 \pm 3.1$ ;  $p < 0.001$ ) and gender analysis showed that the MedD Score was higher in women compared to men ( $28.8 \pm 2.0$  vs  $20.1 \pm 2.5$ ;  $p < 0.001$ ).

In the group of patients with AF the MedD Score was higher in women compared to men ( $24.3 \pm 2.0$  vs  $19.1 \pm 2.2$ ;  $p < 0.001$ ). Comparing women with AF and healthy women, the MedD Score was lower in the AF group ( $24.3 \pm 2.0$  vs  $27.9 \pm 5.6$ ;  $p < 0.001$ ). Similarly, men with AF had a lower adherence to the MedD Score ( $19.1 \pm 2.2$  vs  $21.4 \pm 2.5$ ;  $p < 0.001$ ).

Women with AF were overweight compared to healthy women ( $76.4 \pm 5.0$  vs  $68 \pm 4.5$  kg;  $p < 0.001$ ) and they also had a higher waist circumferences ( $92 \pm 4$  vs  $87 \pm 52$ ;  $p < 0.001$ ) as shown in **Table 1**.

The intake of antioxidants from different categories of food was evaluated and we found that in patients with AF the estimated intake of total antioxidants was higher in women compared to men ( $19.9 \pm 5.6$  vs  $11.2 \pm 7.4$  mmol/d;  $p < 0.001$ ). Healthy women had a higher estimated intake of total antioxidants compared to women that developed AF ( $22.3 \pm 7.1$  vs  $19.9 \pm 5.6$  mmol/d;  $p < 0.05$ ).

The analysis of sources of antioxidants showed that women with AF had a higher intake from vegetables and fruits; on the contrary, men with AF had a higher intake from cereals and coffee. Almost all the patients drank espresso coffee and cappuccino (mainly at breakfast time). Women had a higher intake of tea compared to men. (**Figure 1**). Men had a higher alcohol intake compared to women. The percentage of healthy women that drink wine during meals was higher compared to women with AF (60.5% versus 40 %;  $p < 0.001$ ); on the contrary, the percentage of men that drink wine during meals was lower in healthy control compared to patients with AF (48 versus 53.6%;  $p < 0.01$ ). Intake of olive oil was higher in healthy control. Healthy women had higher intake of olive oil compared to women with AF, and this parameter was correlated with vegetables and legumes.

**Table 2** shows the results from a multiple linear regression model, after checking for age, sex, body

**Table 1** - Clinical characteristics of patients

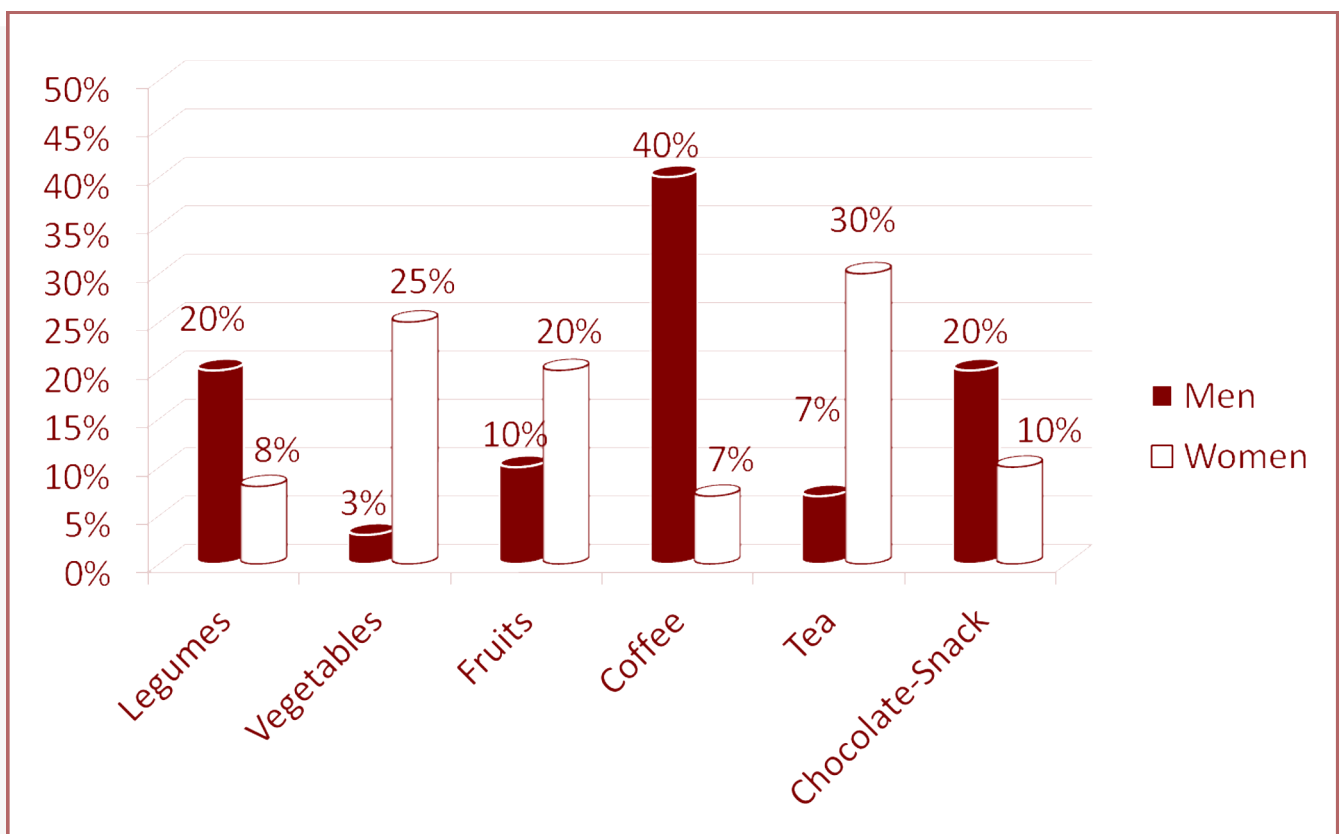
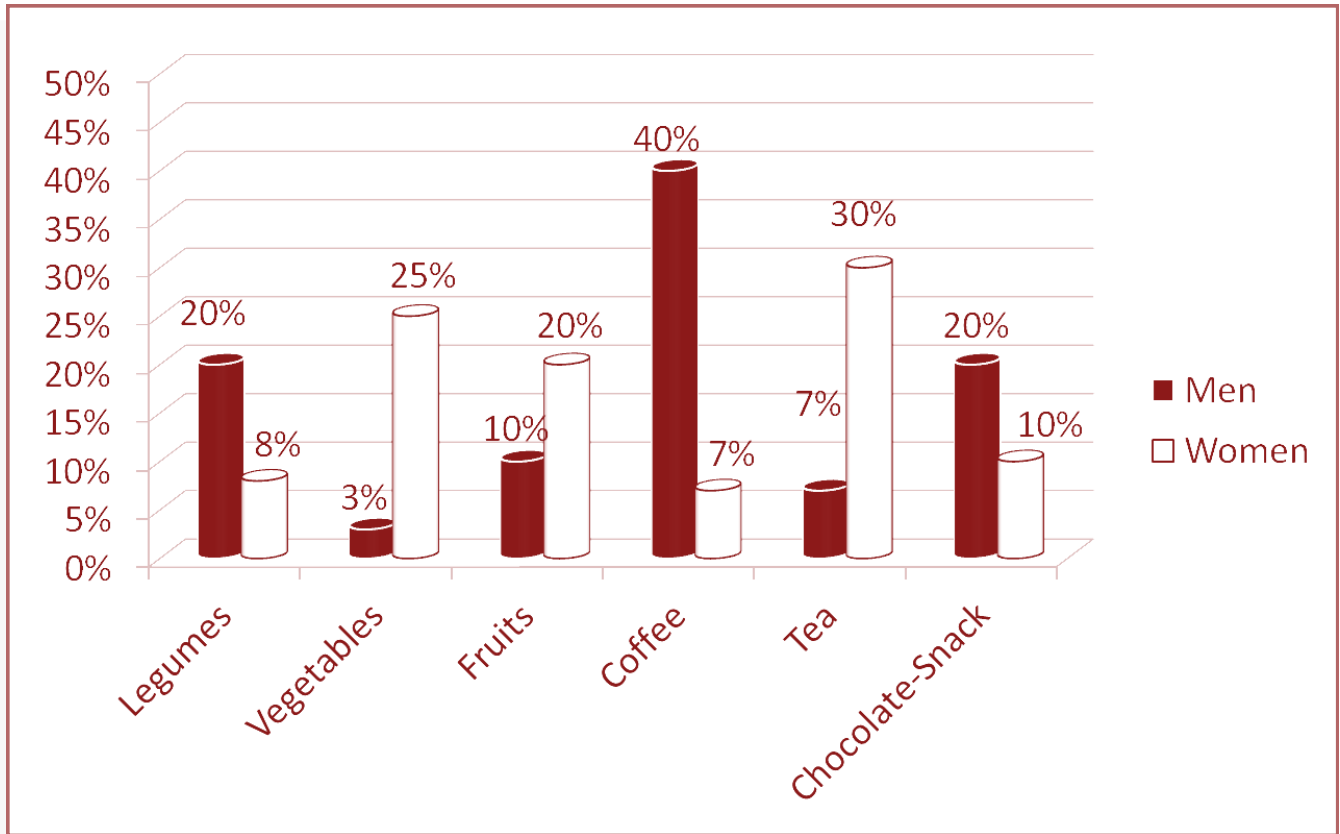
Clinical characteristics	Women with AF	Women without AF	p	Men with AF	Men without AF	p
Number of patients	195	195	n.s.	205	205	n.s.
Mean age (years)	57 ± 5	56 ± 6	n.s.	57 ± 4	57 ± 5	n.s.
Weight (Kg)	76.4 ± 5.0	68 ± 4.5	0.001	90.3 ± 8.0	89.4 ± 7.0	n.s.
Body mass index (mean)	26.4 ± 5.0	24.2 ± 2.5	0.001	27.2 ± 3.8	25.4 ± 4.3	0.001
Waist circumference (cm)	92 ± 4	87 ± 2	0.001	118 ± 7	109 ± 6	0.001
Systolic blood pressure (mmHg)	129 ± 19	127 ± 21	n.s.	128 ± 18	127 ± 23	n.s.
Diastolic blood pressure (mmHg)	82 ± 10	78 ± 18	0.001	86 ± 9	85 ± 7	n.s.

\*Heart rate was measured after conversion of atrial fibrillation. Legend: AF= atrial fibrillation

**Table 2** Results from multiple linear regression analysis evaluating association between Med Score (3), antioxidant levels and spontaneous conversion of atrial fibrillation (outcome) in women and in men with AF

Parameters	Women with AF		Men with AF	
	Beta coefficient + SE	p	Beta coefficient + SE	p
Med Diet Score				
1 <sup>st</sup> quartile (Q1)	-0.5 + 0.6	1.23	-0.9 + 1.1	2.14
2 <sup>nd</sup> quartile (Q2)	1 + 1.76	0.76	1 + 0.97	0.82
3 <sup>rd</sup> quartile (Q3)	1.4 + 1.0	0.052	1.2 + 1.7	0.21
4 <sup>th</sup> quartile (Q4)	2.9 + 1.2	0.001	1.9 + 1.8	0.01
Antioxidants levels				
1 <sup>st</sup> quartile (Q1)	0.23 + 1.75	0.67	0.55 + 1.1	0.83
2 <sup>nd</sup> quartile (Q2)	0.15 + 2.0	0.32	0.25 + 1.87	0.45
3 <sup>rd</sup> quartile (Q3)	0.09 + 1.2	0.21	0.13 + 0.64	0.34
4 <sup>th</sup> quartile (Q4)	3.5 + 1.01	0.001	2.4 + 1.3	0.001
BMI (per 1kg/m <sup>2</sup> )	-1.2 + 0.69	0.003	-1.3 + 0.55	0.002
Waist circumference (per 1 cm)	-1.2 + 0.34	0.042	-1.3 + 0.76	0.037

**Figure 1.** Comparison between different sources of antioxidants evaluated % of the total amount of antioxidants derived from the combinations of individual antioxidants that occur naturally in foods, in men and women with AF.





mass index. A low adherence to the Mediterranean Diet was associated with persistence of atrial fibrillation in women and in men. Women and men with Mediterranean Score in the highest quartile had a higher probability of spontaneous conversion of arrhythmia compared with women and men in the lowest quartile. Low level of antioxidant intake was also associated with an increasing risk of developing AF in women (O.R. 1.9; 95%CI 1.65-3.2;  $P < 0.01$ ).

## Discussion

The main finding of the present study is that patients that developed paroxysmal AF had a lower adherence to the Mediterranean Diet. Gender analysis suggested that women had a higher adherence to the Med Diet and a higher intake of antioxidants from healthy food compared with men.

Moreover, women without AF showed a higher adherence to the Med Diet compared with women that developed AF, suggesting the protective role of a healthy diet in relation to the development of atrial arrhythmia.

Atrial fibrillation is the most common arrhythmia in clinical practice (13). The pathophysiology of AF is complex and is not completely understood, but many studies suggest oxidative stress as a mediator of AF (18). Experimental studies have found the role of oxidative stress in the pathogenesis of AF; however, clinical trials using general antioxidants have not shown the expected therapeutic result (18). Several observational studies have suggested that people with high intakes of fruits, vegetables and olive oil, which are rich in antioxidants, vitamins and flavonoids, experienced lower risk of chronic cardiovascular diseases (1,9). In a previous study we found that lower adherence to a healthy dietary pattern influenced the development of atrial fibrillation and spontaneous conversion of arrhythmia (4). The present paper analyzed gender differences in adherence to the

Mediterranean Diet as part of a study on atrial fibrillation in patients without underlying cardiac disease (4). Women that developed atrial fibrillation had low adherence to the Mediterranean diet and low intake of antioxidants compared to women without AF. Analysis of food intake showed that women with AF had low consumption of fruits and vegetables and olive oil. The beneficial effects of fruits and vegetables are mainly attributed to the antioxidant properties of various phytochemicals and vitamins in these foods. Total antioxidant capacity considers the cumulative, synergistic, and protective activities of all the antioxidants present in food (19). The synergistic effects of antioxidants and olive oil seem to be a key point. Olive oil is strongly related to the consumption of large quantities of vegetables in the form of salads and large quantities of legumes. The combination of olive oil and vegetables increase the bioavailability of antioxidants.

Similarly, the antioxidant effects of wine (especially red) combined with the dietary antioxidants of the Mediterranean diet might have a more beneficial effect on the prevalence of CHD in a Mediterranean population (16,20,21). In Mediterranean countries alcoholic beverages, mainly wine, are consumed with food in 80% of cases (16,20). Previous studies showed that wine drinkers in Mediterranean countries had a healthier diet than beer drinkers, with a higher intake of fruit, vegetables and fiber. The beneficial effects could be related to specific protective chemical polyphenols found in red wine (21,22). In the present population intake of antioxidants from wine is higher in men compared to women, although women more often consume their wine with food.

Healthy control women had a higher intake of wine during meals and a lower intake of alcohol beverages other than wine. The relationship between alcohol intake, specifically wine intake, and synergistic effects with food is complex and needs to be confirmed by a large clinical trial.

Women that developed atrial fibrillation were overweight. It is well known that AF is strongly related with obesity and reduced physical activity. (23,24,25).

Moderate physical activity has been shown to have several physiological benefits that could reduce the incidence of AF in older adults. Physical activity induces and maintains weight loss, lowers resting heart rate and blood pressure, improves glucose control, and improves serum lipoprotein levels and mental well-being. Physical activity may also improve endothelial function and lower systemic inflammation. Each of these is a risk factor for AF (23,24)

The Mediterranean Diet was associated with a healthy lifestyle, less smoking and a high level of physical activity. As previously reported, we found that sedentary patients were more likely to develop atrial fibrillation (18). Our results support the hypothesis that adherence to the Mediterranean Diet is more frequent in subjects that tend to pursue a healthy lifestyle.

### Limitation of the Study

In this kind of study it is not possible to differentiate the dietary effect from other characteristics, such as weight and circumference of the waist and hips. To limit the effects of this bias we selected healthy control patients according to age and gender. However, due to the design of the study we cannot exclude an influence from other parameters. The major limitation of the study was that the dietary habits were self-reported and alcohol intake could be underestimated. Some misclassification of exposure was therefore to be expected.

Another limitation is the estimation of antioxidants from food. We did calculate antioxidants from food categories, but the quantities were derived from a questionnaire. Although at that time we were not able to measure plasmatic levels of antioxidants, we were very accurate in determining quantity and frequency of food.

Moreover, the exact number, duration and timing of asymptomatic AF episodes, as well as the frequency and

type of onset triggers are unknown. Thus, it was impossible to include patients with asymptomatic episodes of AF. This bias is common in studies performed on patients with atrial fibrillation. However, we did select only patients without underlying cardiac disease in order to reduce the probability of previous asymptomatic episodes.

### Conclusions

Women that developed AF had a low adherence to the Mediterranean Diet compared with the healthy control group. Women with low adherence to the Mediterranean Diet also had a less healthy lifestyle that could favor arrhythmia developing. Intake of antioxidants derived from vegetables and fruit and wine during meals was greater in the healthy women. These observations suggest that a healthy lifestyle and high adherence to the Mediterranean diet could prevent episodes of AF in women without underlying cardiac disease.

### Conflict of Interest

No conflict of interest

### References:

1. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008; 337;a1344
2. Trichopoulos A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and overall survival in the elderly. *BMJ* 1995;311:1457-60
3. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: A Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. *Nutr Metab Cardiovasc Dis* 2006;16, 559-568
4. Mattioli AV, Miloro C, Pennella S, Pedrazzi P, Farinetti A. Adherence to Mediterranean diet and intake of antioxidants influence spontaneous conversion of



- atrial fibrillation. *Nutr Metab Cardiovasc Dis.* 2011; 23:115-21
5. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. *BMJ* 2009;338:b2337
  6. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S. The antioxidant vitamins and cardiovascular disease. A critical review of epidemiologic and clinical trial data. *Ann Intern Med* 1995;123:860–72.
  7. Heidemann C, Schulze MB, Franco OH, van Dam RM, Mantzoros CS, Hu FB. Dietary Patterns and Risk of Mortality From Cardiovascular Disease, Cancer, and All Causes in a Prospective Cohort of Women. *Circulation.* 2008;118: 230-237
  8. Dedoussis GV, Kanoni S, Mariani E, Cattini L, Herbein G, Fulop T et al. Mediterranean diet and plasma concentration of inflammatory markers in old and very old subjects in the ZINCAGE population study. *Clin Chem Lab Med* 2008;46:990-6.
  9. A.V.Mattioli, S. Pennella, A. Farinetti. Stile di vita e fibrillazione atriale. *Progress in Nutrition* 2012; 14:87-99..
  10. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation).*Circulation* 2006;114:e257-e354.
  11. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. *Circulation.* 2011;123:e269-367.
  12. Mattioli AV, Bonatti S, Zennaro M, Mattioli G. The relationship between personality, socio-economic factors, acute life stress and the development, spontaneous conversion and recurrences of acute lone atrial fibrillation. *Europace* 2005;7:211-20.
  13. Porrini M, Gentile G, Fidanza F. Biochemical validation of a self-administered semi-quantitative food-frequency questionnaire. *Brit J Nutrition* 1995; 74, 323-333
  14. Mattioli AV, Farinetti A, Miloro C, Pedrazzi P, Mattioli G. Influence of coffee and caffeine consumption on atrial fibrillation in hypertensive patients. *Nutr Metab Cardiovasc Dis.* 2010 Feb 16. [Epub ahead of print] doi:10.1016/j.numecd.2009.11.003
  15. Mattioli AV. Effects of caffeine and coffee consumption on cardiovascular disease and risk factors. *Future Cardiology* 2007;3:203-212
  16. Svilaas A, Sakhi AK, Andersen LF, Svilaas T, Ström EC, Jacobs DR Jr, et al. Intakes of Antioxidants in Coffee, Wine, and Vegetables are Correlated with Plasma Carotenoids in Humans. *J Nutr* 2004;134:562–567
  17. Wolf AM, Hunter DJ, Colditz GA et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol* 1994;23:991–999
  18. Sovari AA, Dudley SC. Antioxidant therapy for atrial fibrillation: lost in translation? *Heart* November 2012; 98: 1615-1616
  19. Yang M, Chung SJ, Floegel A, Song WO, Koo SI, Chun OK. Dietary antioxidant capacity is associated with improved serum antioxidant status and decreased serum C-reactive protein and plasma homocysteine concentrations. *Eur J Nutr* 2013 DOI 10.1007/s00394-012-0491-5
  20. Crozier A, Del Rio D, Clifford MN. Bioavailability of dietary flavonoids and phenolic compounds. *Molecular Aspects of Medicine* 2010; 31:446–467

21. Opie LH, Lecour S. The red wine hypothesis: from concepts to protective signalling molecules. *Eur Heart J* 2007; 28:1683-1693.
22. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Alcohol Consumption and Mortality in Patients With Cardiovascular Disease A Meta-Analysis. *J Am Coll Cardiol* 2010; 55: 1339–47.
23. Mont L, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M, Vidal B, Scalise A, Tejeira A, Berruezo A, Brugada J on behalf of the GIRAFa (Grup Integrat de Recerca en Fibrillacio Auricular) Investigators. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. *Europace* (2008) 10, 15–20 doi:10.1093/europace/eum263
24. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical Activity and Incidence of Atrial Fibrillation in Older Adults. *The Cardiovascular Health Study. Circulation* 2008;118;800-807
25. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: The Danish Diet, Cancer, and Health Study. *The American Journal of Medicine* 2005; 118, 489–495