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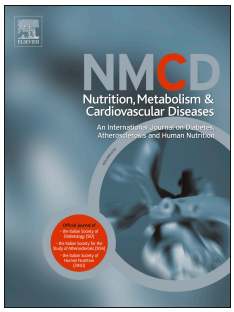

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PII: S0939-4753(20)30227-1

DOI: https://doi.org/10.1016/j.numecd.2020.05.034

Reference: NUMECD 2332

To appear in: *Nutrition, Metabolism and Cardiovascular Diseases*

Received Date: 20 December 2019

Revised Date: 15 May 2020

Accepted Date: 28 May 2020

Please cite this article as: Trevisan M, Krogh V, Grioni S, Mediterranean diet and All-cause mortality: A cohort of Italian men, *Nutrition, Metabolism and Cardiovascular Diseases*, https://doi.org/10.1016/j.numecd.2020.05.034.

Mediterranean diet and All-cause mortality: A cohort of Italian men.

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Abstract

The present study analyzes the relation between diet and all-cause mortality in a cohort of Italian men residing in different regions of Italy.
The cohort was established using the members of the Associazione Nazionale Alpini, a voluntary organization that enlists individuals who have served in the Alpine troup; a mountain warfare infantry corps of the Italian Army.

For the purpose of these analyses a total of 5049 participants were followed for an average of seven years. At baseline information was collected regarding age, education, life style habits, with special emphasis on diet (with the use of a validated dietary questionnaire), smoking and alcohol use. A total of 190 deaths were ascertained. In multivariate analyses the consumption of a Mediterranean type diet was inversely associated with mortality. Additional findings of relevance include: an inverse association between mortality and intake of vegetable fats and proteins, monounsaturated (MUFA) fats of vegetable origins, starch and folic acid. Positive association were evident between mortality and intake of animal fats, MUFA of animal origins and sugar.
This study, focusing on a homogenous cohort characterized by a varied intake and high intake of monounsaturated fats, confirms the inverse association between a Mediterranean type diet and mortality and points out that the nature of the MUFA may be relevant for their effects on health. In addition, the study confirms that fats of animal origins and dietary sugar are associated with an overall deleterious effect on mortality.

Introduction

The relation between Mediterranean diet and health has been widely studied. A number of epidemiological studies have shown that a dietary pattern that emphasizes plant based foods, consumption of fish and poultry, and uses olive oil as the main source of fat, is associated with lower all cause and specific cause mortality. These findings have been summarized in a several meta-analyses (1, 2). The present study was designed to evaluate the association between diet and mortality in Italy, one of the countries where the Mediterranean diet originated. Italy is characterized by a significant geographical variation in dietary patterns and therefore allows to overcome one of the potential limitations of nutritional epidemiological studies (i.e. the relative limited variation of dietary habits in homogenous populations).

Materials and methods

The Alpines Project is a prospective cohort study of Italian men who were recruited among the members of the veteran association of the Alpine corps of the Italian Army. The aim of the study was to create a large cohort of men residing in different parts of Italy, a country characterized by a high variability in dietary habits. The purpose of study is to investigate the role of diet and lifestyle factors on overall mortality. On December 1992 we delivered 365,000 questionnaires to the members of the National Alpine Association. 12,384 men returned the completed questionnaire but 110 participants were eliminated because large portions of the questionnaire were missing for a total of 12,274.

Follow up

The follow-up procedure was based on requesting information about the vital status of the study participants through the leaders of the local chapters of the Alpine Association. The information received was validated through a validation study conducted in two areas of the country covered by regional cancer registries.

For the mortality follow-up, information about the 12,274 respondents was sought from 2017 local chapter leaders. 74.5% of the group leaders responded providing information for a total of 7054 participants. For 1134 participants the vital status was unknown. 111 Additional participants were eliminated because the ratio of total energy intake to basal metabolic rate was at either extreme of the distribution (cut-offs first and last half percentiles). 324 participants were eliminated because of missing variables included in the analytical model and 539 were eliminated from these analyses because they reported a disease at baseline (Myocardial Infarction, stroke, diabetes, chronic hepatitis, cancer). After all these exclusions, 5046 men remained eligible for the study. The mean age of the cohort at recruitment was 48.6 years and during the follow up period a total of 190 participants were reported deceased and available for these analyses.

The questionnaire was designed to ascertain dietary and drinking habits. In addition, the questionnaire elicited information regarding residence, marital status, educational attainment, occupation, family and personal history of disease, use of medication and smoking habits. Participants were asked to self-report height and weight.

The dietary self-administered questionnaire was developed by identifying the food items that explain at least 95% of the nutrients source and variation in the Italian diet. The sources for the identification of the food items were two epidemiological nutritional studies

that enlisted participants throughout the Italian national territory (3-5). The dietary intake was assessed through 130 items. For each food, participants were asked to select the medium consumption over the past year, using a scale of 9 ranges of frequency, from "never" to "two times per day" and the quantity was investigated through the three choices "less", "equal" or "more" than the medium portion indicated (in grams or by a standard size). The questionnaire was also included a detailed section about alcohol amount and patterns of consumption, with questions about wine (red and white), beer and spirits. Data of frequency and quantity of food consumption were elaborated using an ad hoc developed software to obtain the daily nutrient intakes from the Italian Food Composition Table for Epidemiological Studies (6). The adherence to Mediterranean diet was estimated using the Italian Mediterranean Index, developed by adapting the Greek Mediterranean Index (7) to the eating behaviors of the Italian population. The score is based on 11 items: high intake of six typical Mediterranean foods (pasta, typical Mediterranean vegetables, fruit, legumes, olive oil and fish), low intake of four non Mediterranean foods (soft drinks, butter, red meat and potatoes) and moderate alcohol consumption. Participants received one point for food intake above the median of intake for typical Mediterranean food and 0 point for consumption below the median. For alcohol use participants received 1 point for intake up to 1 serving/day (12gr. alcohol); abstainers and persons who consume more than 1 serving/day receive 0. Possible total score range from 0 to 11.

Smoking habits were categorized as never smokers, former smokers, smokers of 1-14 cigarettes /day, 15-24, and 25+ cigarettes/day.

Statistical analysis

Analyses were performed with Stata version 14.0 (College Station, TX). Dietary nutrients were adjusted for energy intake using the regression-residual method (8). Nutrients intake was categorized into quartiles, based on the distribution of intake in the whole cohort, with lowest quartile as reference. Association between risk factors and mortality was analyzed using the unconditional logistic regression model. In the multivariate model the adjustments were made for age, years of education (≤5, 8-12, >12 years), smoking history and hypertension. The Italian Mediterranean Index was analyzed as categorical variable and trend test was calculated using the median values for quantiles modeled as a single continuous variable.

Results

After a mean follow-up of 7 years 291 deaths for all causes were reported. Approximately 77% of the study participants were at least 40 years old and 75% completed an 8th grade education. The great majority of the study participants were married and the approximately 45% were former smokers. In terms of alcohol consumption 88% reported consuming alcoholic beverages and 63% reported a BMI of 25 or greater (Table 1)

Table 1 Baseline characteristic of cohort (n=5049)

Variable	n. of subjects	%	n. of events
Age *(n=5046)*			
19-30	442	8.76	1
30-40	835	16.55	3
40-50	1242	24.61	17
50-60	1418	28.10	46
> 60	1109	21.98	123
Educational level *(n=5046)*			
Lower (≤ 5 years)	1230	24.38	82
Intermediate (8-12 years)	1712	33.93	49
Advanced (> 12 years)	2104	41.70	59
Marital status *(n=5019)*			
Married	4082	81.33	156
Unmarried	753	15.00	9
Widower	103	2.05	18
Divorced	81	1.62	5
Smoking habits *(n=5046)*			
Never smoker	1922	38.09	48
Former smoker	2155	42.71	96
1-14 (cigarettes/day)	517	10.25	22
15-24	349	6.92	19
>25	103	2.04	5
Alcohol consumption *(n=5046)*			
None	648	12.84	38
Moderate drinkers (< 2 drinks/day)	1334	26.44	36
Heavy drinkers (> 2 drinks/day)	3064	60.72	116
BMI kg/m² *(n=4955)*			
<25	1883	38.00	69
25-30	2537	51.20	83
>30	535	10.80	31

Table 2 summarizes the dietary habits of the cohort. This cohort is characterized by a high total fat intake and, as expected, monounsaturated fats represent the major source of fat in this population with oleic acid representing the most significant source of monounsaturated fats and the single most consumed source of fat.

In terms of % calories from the different sources: Protein represented on average 15%, Carbohydrates 43% and Fat 34 % of calories. Monounsaturated fats represented 14.5% and oleic acid 13.6% of total calories.

The average Mediterranean Index score for this cohort was 4.3.

Table 2 Dietary characteristics of the study population (n=5049)

Nutrient	Mean	SD	10th percentile	90th percentile
Protein g/day				
Total	88.78	34.77	49.95	132.44
Animal	58.82	29.23	26.96	95.46
Vegetable	29.61	9.45	18.70	46.32
Fat g/day				
Total	91.71	39.95	45.94	141.96
Animal	55.51	30.94	22.63	93.86
Vegetable	35.22	17.12	14.78	58.49
Saturated fatty acids	34.31	17.80	14.97	56.99
Monounsaturated fatty acids	39.58	16.79	19.82	61.76
Mono from animal	18.12	9.94	7.67	30.39
Mono from vegetables	21.36	11.41	8.14	36.88
Polyunsaturated fatty acids	11.74	5.05	5.92	18.59
Oleic acid	37.04	15.77	18.41	57.65
Linoleic acid	9.85	4.69	4.88	15.70
Linolenic acid	1.39	0.61	0.70	2.21
Cholesterol mg/day	326.28	162.87	150.05	529.68
Carbohydrates g/day				
Total	265.95	88.53	163.23	379.38
Starch	181.09	61.04	107.75	258.33
Sugars	84.72	43.56	40.01	137.70
Fiber g/day	18.47	7.11	10.77	27.42
Alcohol g/day	40.32	38.05	0.00	88.30
Energy kcal/day	2460.34	786.32	1526.50	3475.51
Folic acid µg/day	293.52	124.15	161.97	442.49
Mediterranean score	4.27	1.63	2.00	6.00

Table 3 shows the Relative Risk (95% CI) for all-cause mortality in relation to daily nutrients intake and the Italian Mediterranean Index in the cohort. The nutrients analyzed were included separately in the models. The data focus on 5049 participants free of disease at baseline and the models include adjustment for age, education, and smoking.

Increasing intakes of animal fats and sugar were associated with a significant increase in mortality, while increasing intakes of vegetable proteins and vegetable fats were significantly inversely related to mortality.

For consumption of MUFA, the observed association is negative but does not reach statistical significance. However, consumption of MUFA from vegetable sources was significantly and inversely related to mortality, while consumption of MUFA from animal sources was positively related to mortality. Intake of starch and folic acid was inversely associated with risk of mortality. No significant association was found between alcohol intake and mortality. Finally, the Italian Mediterranean Index was associated with a significantly lower risk of mortality for the 4th quartile compared with the first and with a statistically significant inverse trend.

Table 3: Relative risk (95% CI) for all-cause mortality in relation to daily nutrients intake and the Italian Mediterranean Index (n=5585)

Nutrients	Quartile of Intake (energy-adjusted, residual method)				p for trend
	1	2	3	4	
Total protein g/day					
Deaths	52	46	44	48	
Relative risk (95% CI)	1.00	0.84 (0.55-1.29)	0.95 (0.62-1.46)	1.03 (0.68-1.58)	0.777
Animal protein g/day					
Deaths	49	45	43	53	
Relative risk (95% CI)	1.00	0.87 (0.56-1.34)	0.91 (0.59-1.41)	1.20 (0.79-1.82)	0.354
Vegetable protein g/day					
Deaths	62	53	42	33	
Relative risk (95% CI)	1.00	0.90 (0.60-1.34)	0.69 (0.45-1.05)	**0.58 (0.37-0.91)**	**0.009**
Total fat g/day					
Deaths	53	53	37	47	
Relative risk (95% CI)	1.00	1.05 (0.70-1.59)	0.92 (0.59-1.43)	1.32 (0.86-2.03)	0.303
Animal fat g/day					
Deaths	44	43	58	45	
Relative risk (95% CI)	1.00	1.02 (0.65-1.60)	**1.67 (1.10-2.55)**	1.39 (0.89-2.17)	**0.044**
Vegetable fat g/day					
Deaths	57	60	37	36	
Relative risk (95% CI)	1.00	1.12 (0.75-1.67)	0.68 (0.43-1.06)	0.69 (0.44-1.08)	**0.031**
Saturated fatty acids g/day					
Deaths	48	43	57	42	
Relative risk (95% CI)	1.00	0.89 (0.57-1.38)	1.56 (1.03-2.36)	1.21 (0.78-1.90)	0.128
Monounsaturated fatty acids (MUFA) g/day					
Deaths	61	48	43	38	
Relative risk (95% CI)	1.00	0.89 (0.59-1.34)	0.90 (0.59-1.38)	0.79 (0.51-1.22)	0.311
MUFA animal origin g/day					
Deaths	49	32	63	46	
Relative risk (95% CI)	1.00	0.66 (0.41-1.06)	**1.80 (1.20-2.70)**	1.34 (0.87-2.06)	**0.018**
MUFA vegetable origin g/day					
Deaths	61	52	43	34	
Relative risk (95% CI)	1.00	0.83 (0.56-1.25)	0.70 (0.46-1.07)	**0.59 (0.38-0.93)**	**0.017**
Polyunsaturated fatty acids g/day					
Deaths	60	40	39	51	
Relative risk (95% CI)	1.00	0.66 (0.43-1.02)	0.79 (0.51-1.23)	1.14 (0.76-1.72)	0.339
Cholesterol mg/day					
Deaths	56	37	46	51	
Relative risk (95% CI)	1.00	0.73 (0.47-1.13)	1.03 (0.68-1.57)	1.36 (0.99-2.06)	0.091

Total Carbohydrate g/day					
Deaths	61	50	36	43	
Relative risk (95% CI)	1.00	0.83 (0.56-1.25)	0.64 (0.41-1.00)	1.05 (0.69-1.60)	0.764
Starch g/day					
Deaths	68	45	43	34	
Relative risk (95% CI)	1.00	0.68 (0.45-1.02)	**0.64 (0.42-0.96)**	**0.61 (0.39-0.94)**	**0.015**
Sugars g/day					
Deaths	52	44	44	50	
Relative risk (95% CI)	1.00	0.81 (0.53-1.25)	1.00 (0.65-1.53)	1.44 (0.94-2.20)	0.064
Fiber g/day					
Deaths	55	43	45	47	
Relative risk (95% CI)	1.00	0.77 (0.50-1.19)	0.96 (0.63-1.48)	0.90 (0.60-1.39)	0.879
Folic acid µg/day					
Deaths	62	45	47	36	
Relative risk (95% CI)	1.00	0.66 (0.44-1.00)	0.79 (0.53-1.20)	**0.59 (0.38-0.92)**	**0.041**
Alcohol g/day					
Deaths	36	44	50	60	
Relative risk (95% CI)	1.00	0.90 (0.56-1.45)	0.81 (0.51-1.29)	0.84 (0.53-1.31)	0.453
Mediterranean Index					
Deaths	75	45	37	33	
Relative risk ** (95% CI)	1.00	0.93 (0.63-1.40)	0.79 (0.52-1.21)	**0.62 (0.40-0.96)**	**0.026**

Adjusted by age, education, smoking (never, former, 1-14 cigarettes/day, 15-24 cigarettes/day, more than 25 cigarettes/day, hypertension.
**Mediterranean index is also adjusted by energy (kcal/day)

Discussion

Our findings, from a national cohort of men residing in a country with strong regional differences in dietary habits and characterized by a high intake of monounsaturated fats, indicate that the consumption of a Mediterranean diet (high consumption of vegetables, fruit, legumes, olive oil and fish.) is associated with significantly lower all-cause mortality. The individual component of this dietary pattern (vegetable fats and proteins, starch and folic acid) were all individually associated with significantly lower mortality. For monounsaturated fats, only those of vegetable origin were associated with lower mortality. On the contrary the consumption of animal fats and sugar were associated with higher mortality.

The effects of the Mediterranean diet and its component have been the subject of intensive investigation, since the work of Ancel Keys in the Seven Countries Study (9-11). The majority of the studies that have analyzed the health effects of the Mediterranean diet have focused on cardiovascular disease, including many epidemiological studies and several randomized clinical trials (1,2), but the potential benefits of the Mediterranean diet have been extended to other chronic conditions (1,12-14). A recent meta-analysis confirmed the inverse association between the use of a Mediterranean type diet and lower all-cause mortality (2) This comprehensive reviews identified thirty articles, most of these studies were conducted in countries that are not characterized by a traditional Mediterranean diet (USA, Northern Europe or Australia). Two multicenter studies were conducted in Europe and included both northern and southern European countries. 8 studies were conducted in Mediterranean countries (Italy, Spain and Greece). The findings across studies in this meta-analysis were remarkably consistent, however some heterogeneity in the results were found between studies conducted in the US and Europe and the benefits of the diet appeared to be stronger in Mediterranean countries compared to western and northern European countries. One of the potential reasons is the fact that adherence to the traditional Mediterranean diet is greater in countries were a Mediterranean type diet is the way of life.

In terms of Italian studies, two were conducted in a limited and more homogenous part of the country (northern regions), traditionally characterized by a northern European type diet (15) or focused only on elderly individuals (16). A multicenter longitudinal study found a significant inverse relationship between adoption of a Mediterranean diet pattern and the incidence of stroke (17).

Our study focuses on a group of men with a broad age range at baseline and residing throughout the country. The wide geographic distribution of our sample allowed the analyses to be conducted in a group of individuals characterized by a varied intake. Our study confirms the findings with regard to the Mediterranean diet score and expand them by identifying that monounsaturated fats from different origins may have a different relationship with mortality. It is not clear whether this association is due to the source of the MUFA, the action of the other nutrients (animal proteins and fats) associated with the consumption of food of animal origin and rich in MUFA (red meat, processed meat, whole milk products), or that vegetal MUFA is just a marker for a healthy life style. It is interesting to note that the position of oleic acid in the triglycerides may differ between vegetable (higher proportion in sn-2) and animal sources (higher proportion in sn-1 and sn-3) and that the sn-2 position is associated with higher absorption and potentially biological effects (18)

In addition to the beneficial effects of the Mediterranean diet and its component, our study confirms that the consumption of animal fats and animal products is associated with increased all-cause mortality (19,20). The relationship between animal fats and mortality has been the source of some controversy. A number of epidemiological studies have been unable to find a significant association. The inability of several epidemiological studies to find a positive association between animal fats and health may have been the result of the limited variability in the diets of homogenous populations. The null findings of observational studies (21) contrast with experimental and controlled dietary intervention studies that are concordant in showing that a diet rich in animal and saturated fats has deleterious effects on CVD risk factors and clinical endpoints (22).

Of interest is the inverse relationship between folic acid and mortality. Major sources of folic acid are leafy green vegetables, citrus fruits, legumes, all important components of the Mediterranean diet

Our study has a number of limitations, including its observational nature. Like all nutritional studies, our study relies on self-reported measures of diet and other life style habits and risk factors. Other limitations include the availability of only one measure of diet and the selective nature of our sample. In terms of representation of Italian men, it should be noted, that until recently, in Italy the military service was compulsory therefore the veterans of the armed forces are representative of the general population. However, the limited

number of participants, compared to the available veterans limits the generalizability of our sample.

Our study has strength as well, including the use of a dietary questionnaire developed by identifying 95% of the consumption and variability of nutrient in a national sample. The major strength of our study is the nature of our sample, derived from a homogenous population characterized by a significant variability in dietary habits. Our study, confirms that, when non hampered by a limited variability, the negative effects of a diet rich in animal sources, fats and protein, are evident and that, conversely, a diet reach in in vegetable sources is associated with beneficial effects on mortality. Finally, the source of MUFA may be relevant in determining their health effects.

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Mediterranean diet and All-cause mortality: A cohort of Italian men.

Highlight for the Reviewer

We believe that the best way to study the relationship between diet and health is ain an homogenous population characterized by a varied intake. In this regard Italy represent an ideal place for nutritional epidemiology because the diet of Italians varies significantly through the national territory: with the southern regions being traditionally characterized by the typical Mediterranean diet (olive oil as the main source of fat, vegetables, fish, legumes) and the northern regions being characterized by a more "continental" northern European (butter as an important source of fat, dairy products and meats).

Or findings confirm the beneficial effects of the Mediterranean diet, and expand the current knowledge by pointing out that the source of the monounsaturated (MUFA) fats in the diet may be relevant as we find an inverse association with mortality only for MUFA of vegetable origin. In addition our study confirm the benefits of vegetable protein and the deleterious effect of animal, saturated fats and dietary cholestol.

There are no conflicts for any of the authors