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A priori-defined Mediterranean-like dietary pattern predicts cardiovascular events better in north Europe than in Mediterranean countries☆

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ABSTRACT

Background: The Mediterranean Diet (MD) is a model of healthy eating contributing to a favorable health status, but its clinical usefulness is still debated. The aim of this study was to relate the adherence to MD with the incidence of cardio/cerebro-vascular events (VEs) in north and south European participants of the IMPROVE study.
Methods: IMPROVE is an observational, longitudinal, prospective cohort study involving 3703 individuals from five European countries (Finland, Sweden, Netherlands, France and Italy). The study end-point was the incidence of the first combined cardio/cerebro-vascular event occurring during 36-months follow-up. At baseline, a dietary questionnaire about the usual intake during the year preceding enrollment was administered. Based on 7 nutritional items, a MD Score was constructed in which minimal adherence was 0 and maximal adherence was 7.
Results: Latitude was the strongest determinant of MD score ($p < 0.001$). VEs occurred in 215 participants. The incidence of VEs was the highest in subjects with MD score 0–1, lower in those with score 2–3 and the lowest in those with score ≥ 4. MD score remained significantly associated with subsequent VEs after adjustment for confounders (hazard ratio for one-point increment of the score = 0.75, $p < 0.001$) and the association was stronger in northern than in southern countries ($p = 0.04$ for MD Score × latitude interaction).
Conclusions: The MD adherence score based on a simple dietary questionnaire detects changes of risk of VEs. According to our findings north Europeans appear to benefit most from VE-prevention when their diet is altered to the MD diet.

Abbreviations: MD, Mediterranean Diet; CAD, Coronary artery disease; cIMT, carotid intima media thickness; VEs, Vascular Events; VRFs, vascular risk factors; TIA, transient ischemic attack; hs-CRP, high sensitive C-Reactive Protein.

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1. Introduction

Mediterranean Diet (MD) is a model of healthy eating, known for its contribution to a favorable health status and a better quality of life [1]. MD is based on high consumption of olive oil, legumes, unrefined cereals, fruits, vegetables, moderate/high consumption of fish, moderate consumption of dairy products (mostly cheese and yogurt), wine (especially during meals), and low consumption of meat and meat products [2].

Several studies have documented a positive association between chronic diseases and single foods/nutrients not included into MD such as meat [3], and a negative association with those close to MD (fruit and vegetables [4], diet antioxidants [5]). Based on the results of the Seven Countries Study [6], Trichopoulou et al. conducted an observational prospective study in a large Greek cohort investigating the capacity of a 10-point scale MD adherence score to predict the overall and coronary artery disease (CAD) mortalities [7]. The authors showed that the adherence to MD (rather than to some of its individual components) was inversely associated with coronary death. A meta-analysis of prospective cohort studies on 4,172,412 subjects confirmed these findings and the authors proposed a nine item literature-based MD score that may predict the cardiovascular (CV) risk at the individual level [8]. In the present study, we took advantage of the large IMPROVE study, carried out in 5 European countries with major differences in dietary behavior, to investigate the association of a seven item MD adherence score with the incidence of cardio- and cerebro-vascular events (VEs) in north and south Europe.

Table 1
Patient's characteristics according to classes of MD score.

Characteristics	Missing data	MD score 0–1 (N = 1098)	MD score 2–3 (N = 1868)	MD score 4–7 (N = 737)	P-trend
Latitude					
Kuopio	0	472 (43.0)	520 (27.8)	56 (7.6)	
Stockholm	0	177 (16.1)	291 (15.6)	64 (8.7)	
Groningen	0	319 (29.1)	191 (10.2)	17 (2.3)	
Paris	0	68 (6.2)	275 (14.7)	158 (21.4)	<0.0001
Milan	0	37 (3.4)	282 (15.1)	234 (31.8)	
Perugia	0	25 (2.3)	309 (16.5)	208 (28.2)	
Vascular risk factors					
Framingham risk score	0	27 (19, 41)	22 (14, 33)	18 (11, 28)	<0.0001
European score	0	5.4 (3.2, 9.0)	3.8 (2.3, 6.7)	2.9 (1.8, 5.1)	<0.0001
Male	0	580 (52.8)	919 (49.2)	275 (37.3)	<0.0001
Age	0	64.8 ± 5.4	63.9 ± 5.31	63.9 ± 5.7	0.0001
BMI (kg/m^2)	3	28.4 ± 4.43	27.18 ± 4.22	25.83 ± 3.64	<0.0001
Waist/hip ratio	11	0.93 ± 0.09	0.92 ± 0.09	0.9 ± 0.09	<0.0001
Diastolic BP (mmHg)	5	84 ± 10	82 ± 10	79 ± 9	<0.0001
Systolic BP (mmHg)	5	147 ± 18	142 ± 18	135 ± 18	<0.0001
Hypertension	2	844 (76.9)	1288 (69.0)	420 (57.0)	<0.0001
Diabetes mellitus	0	375 (34.2)	425 (22.8)	113 (15.3)	<0.0001
Hypercholesterolemia	4	610(55.7)	1338(71.7)	633(85.9)	<0.0001
Hypertriglyceridemia	2	236(21.5)	483(25.9)	235(31.9)	<0.0001
Hypoalphalipoproteinemia	2	160 (14.6)	248 (13.3)	80 (10.9)	0.024
Smoking habits	72				
Never smokers		498 (45.4)	878 (47.0)	407 (55.2)	
Former smokers		398 (36.2)	727 (38.9)	246 (33.4)	<0.0001
Current smokers		202 (18.4)	263 (14.1)	84 (11.4)	
Pack-years	72	20 (9.0, 33.2)	17 (7.8, 28.1)	16.3 (7.5, 30.0)	0.03
Family history of:					
Coronary artery disease	3	738 (70.7)	1170 (64.7)	407 (57.8)	<0.0001
Cerebrovascular disease	3	374 (34.1)	689 (36.9)	259 (35.1)	0.49
Peripheral vascular disease	3	118 (10.7)	236 (12.6)	89 (12.1)	0.3
Social class	307				
White collars		322 (32.0)	743 (42.9)	314 (47.7)	
Service workers		374 (37.2)	562 (32.4)	202 (30.7)	<0.0001
Manual workers		309 (30.7)	428 (24.7)	142 (21.6)	
Study years		10.0 ± 3.4	10.6 ± 4.1	10.5 ± 4.2	0.002
Biochemical variables					
Total cholesterol, mmol/L	16	5.32 ± 1.11	5.47 ± 1.12	5.8 ± 1.12	<0.0001
HDL cholesterol, mmol/L	16	1.23 ± 0.36	1.26 ± 0.36	1.32 ± 0.37	<0.0001
Triglycerides, mmol/L	16	1.31 (0.94, 1.91)	1.31 (0.94, 1.91)	1.28 (0.9, 1.8)	0.09
LDL cholesterol, mmol/L	81	3.39 ± 0.96	3.52 ± 1.02	3.83 ± 0.97	<0.0001
Uric acid, μmol/L	16	320 (273, 369)	310 (263, 357)	298 (253, 352)	<0.0001
hs-CRP, mg/L	11	2.1 (0.9, 3.9)	1.8 (0.8, 3.5)	1.6 (0.6, 3.1)	<0.0001
Blood glucose, mmol/L	12	6.26 ± 1.82	5.9 ± 1.64	5.43 ± 1.15	<0.0001
Creatinine, μmol/L	17	82 (71, 93)	79 (69, 90)	75 (65, 88)	<0.0001
Food items					
Fish (portions/week)	13	1.3 ± 0.8	1.8 ± 1.1	2.6 ± 1.4	–
Wine (dl/day)	9	0.6 ± 1.6	1.2 ± 2	1.5 ± 2	–
Meat (portions/week)	14	4.4 ± 1.6	3.6 ± 1.8	2.7 ± 1.6	–
Fruits (portions/day)	5	1.7 ± 0.9	2.2 ± 1.3	3.2 ± 1.7	–
Milk (dl/day)	12	3.9 ± 2.8	2.4 ± 2.3	1.6 ± 2.1	–
Eggs (Number/week)	14	2.2 ± 1.7	1.2 ± 1.1	0.8 ± 0.7	–
Mostly used fat					
Olive oil	5	109 (9.93)	942 (50.43)	663 (89.96)	–
Margarine	5	595 (54.19)	479 (25.64)	34 (4.61)	–
Seed oil	5	235 (21.40)	299 (16.01)	26 (3.53)	–
Other fat	5	159 (14.48)	148 (7.92)	14 (1.90)	–

Values are mean ± SD, or median (interquartile range) or n (%). p Values were calculated by linear regression or by chi square for trend.

2. Material and methods

A summary of design, objectives, eligibility criteria, methods, baseline characteristics, ultrasonographic variables and type and numbers of VEs in the IMPROVE Study have been reported [9–11]. Briefly, IMPROVE is an observational, longitudinal, prospective cohort study that enrolled 3703 patients (1774 men, 1929 women, aged 55–79 years) with ≥3 vascular risk factors (VRFs) free from VEs. Participants were recruited from January 2004 to May 2005 in seven centers in 5 European countries: Finland (n = 1048; 2 centers), Sweden (n = 532), the Netherlands (n = 527), France (n = 501) and Italy (n = 553 in Milan and 542 in Perugia). 36 months follow-up was attained by 93.7% of participants. The combined endpoint included angina pectoris, myocardial infarction, cardiovascular death, ischemic stroke, transient ischemic attack (TIA) and revascularizations of coronary or peripheral arteries. The criteria of diagnosis of VEs have been previously described [10,11]. The study complies with the Declaration of Helsinki. Five local ethics committee approved the research protocol. Each participant provided informed consent for general participation in the study and a separate consent for genotyping.

2.1. The IMPROVE MD score

Dietary intake maintained during the year preceding enrollment was assessed by a semi-quantitative dietary questionnaire, administered by trained personnel. Since the amount and type of vegetables, legumes, nuts and cereals consumed differ among populations [12], the items included in the questionnaire were limited to foods freely available in all the countries involved. We created a MD adherence score analogous to the Greek Mediterranean Index [7], since this index was inversely associated with the incidence of stroke in a recent Italian study [13]. Scoring was based on intake of 7 items: fruits, fish, wine, olive oil, meat, milk and eggs. For fruit or fish, high consumption (top tertile of their distributions, i.e. fruit ≥3 servings/day and fish >2 times/week) received one point, other intakes received 0 points; for meat, eggs or milk a low intake (bottom tertile of their respective distributions, i.e. meat <2 times/week, eggs ≤1 times/week, milk ≤3 dL/day) received one point. A predominant consumption of olive oil, rather than of other types of fat, and a moderate consumption of wine (1–2 glasses/day) also received one point. Based on the scale obtained, score 0 indicates minimal adherence and score 7 maximal adherence to the MD.

2.2. Statistical analysis

Quantitative variables are summarized as means ± standard deviation (SD), or median (interquartile range) when appropriate. Variables with skewed distributions were log-transformed before analysis. Baseline characteristics of subjects, stratified by MD score categories, were compared by linear regression and chi-square for trend, as appropriate. Multivariable linear regression with stepwise selection was employed to identify independent predictors of the MD score, and the interaction between latitude and each predictor was also tested. The association between MD score and VEs was assessed by three Cox models: *Model-1*: unadjusted; *Model-2*: adjusted for age, gender and stratified by latitude; *Model-3*: as model 2 plus lifelong exposure to cigarette smoking (pack-years), body mass index (BMI), education (as indexed by years of school), physical activity, occupation (categorized as: 1, white collars; 2, service workers and 3, manual workers), plasma concentrations of LDL and HDL cholesterol, triglycerides, glucose, high sensitive C-Reactive Protein (hs-CRP), creatinine, pulse pressure, antiplatelet and statin treatments. Kaplan-Meier curves stratified by classes of MD score were also computed. In subgroup analysis an interaction term was included in the Cox models. All tests were two-sided. Analyses were carried out by using the SAS statistical package v. 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Compliance with and determinants of the MD score

Patient's characteristics according to the MD adherence score are presented in Table 1. A score >1 was observed in >90% of the patients in Perugia, Milan and Paris, but only in the 46% of patients in Groningen, Stockholm and Kuopio. The lowest average MD adherence score was found in Groningen (mean ± SD, 1.3 ± 1.1) and in Kuopio (1.7 ± 1.1). Intermediate values were in Stockholm (2.1 ± 1.2) and in Paris (2.9 ± 1.3), whereas the average MD score in Milano and Perugia was >3. With univariate analysis (Table 1), the MD score was negatively and significantly associated with almost all traditional VRFs. Using multivariable analysis, latitude was the strongest independent determinant of MD score (Table 2). Social and behavioral variables, such as education, occupation, physical activity and smoking habits as well as hs-CRP, HDL-cholesterol, BMI, pulse pressure, statin and insulin treatment were also independently associated with MD score (Table 2). A significant interaction between education (a social class index) and latitude was found (p = 0.01), indicating that the dependence of MD score on social class is stronger in northern than in southern countries, the average MD score change for each year of school being 0.06 in Sweden, 0.03 in Finland and 0.016 in Italy.

Table 2
Variables independently associated with MD score by multivariable linear regression with stepwise selection.

Variables	Beta[a]	SE	p Value
Latitude (degrees)	−0.09	0.003	<0.0001
Education (study years)	0.03	0.01	<0.0001
Physical activity (1 step)	0.11	0.03	0.0003
Use of antiplatelet agents	0.19	0.06	0.0007
Log hs-CRP (mg/L)	−0.14	0.04	0.0009
HDL-cholesterol (mmol/L)	0.20	0.06	0.002
Body mass index (Kg/m^2)	−0.02	0.01	0.002
Statin treatment	0.12	0.04	0.006
Pack-years of cigarette smoking	−0.003	0.001	0.009
Creatinine (μmol/L)	−0.003	0.001	0.02
Pulse pressure (mmHg)	−0.004	0.002	0.02
Insulin treatment	−0.25	0.11	0.03
Occupation (white collars)	0.10	0.05	0.03

[a] Beta values indicate change in MD score associated with a unit increment of the predictor. Variables not significantly associated were: sex, age, blood glucose, triglycerides, uric acid, WBC count, family history of CHD, CVD and PVD and other pharmacological treatments (Beta blockers, calcium antagonists, ACE inhibitors, sartans, diuretics, insulin, estrogens, statin, fibrates and fish-oil).

3.2. MD score and vascular events

Among the 3703 subjects enrolled in the IMPROVE Study, 215 (7.96%) developed a first VE within the 36 months follow-up (see Table 1 in Ref [14]. Among these, 125 were cardio-VEs; 73 were cerebro-VEs and 17 were peripheral-VEs.

Fig. 1 of Ref [14] shows the Kaplan-Meier incidence curves of the combined endpoint, and of cardio- and cerebro-VEs, stratified by MD adherence score classes. Regardless of the endpoint considered, the rate of events was the highest in subjects with score 0–1; lower in those with score 2–3 and the lowest in those with score 4–7. The MD score remained significantly associated with the combined endpoint also after stratification by latitude and adjustment for potential confounders (Table 3, Model 2 and 3). Similar results were obtained when cardio- and cerebro-VEs were analyzed separately (Table 3).

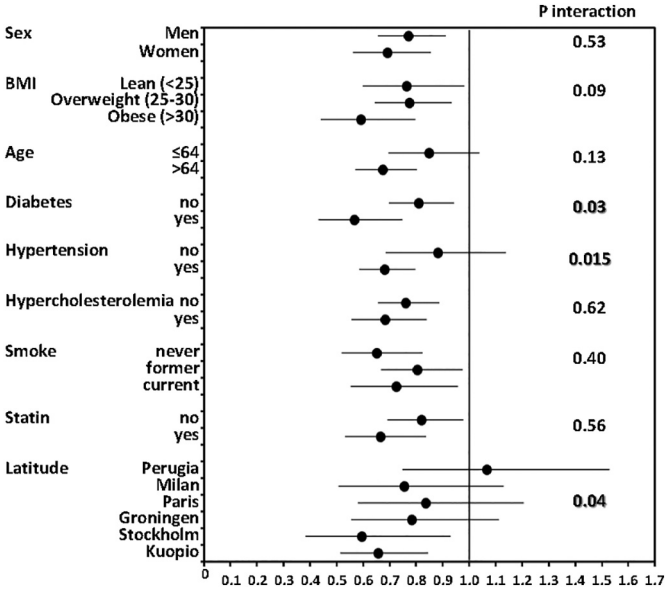

Fig. 1. Hazard ratios for combined cardiovascular events associated with one point increase of MD score: subgroups analysis. Horizontal lines represents 95%CI, adjusted for covariates in Model 3 (see Methods), excluding the respective stratification variables.

Table 3
Association between MD score and vascular events: multivariable adjusted Cox models.

	MD-score	Combined events (n = 215)			Cardiovascular events (n = 125)			Cerebrovascular events (n = 73)		
		Events/subjects	HR (95% CI)	p-Value	Events/subjects	HR (95% CI)	p-Value	Events/subjects	HR (95% CI)	p-Value
Model 1	0–1	101/1098	1		58/1098	1		32/1098	1	
	2–3	94/1868	0.55 (0.41, 0.73)	<0.0001	56/1868	0.58 (0.40, 0.84)	0.004	33/1868	0.59 (0.36, 0.96)	0.03
	4–7	20/737	0.29 (0.18, 0.47)	<0.0001	11/737	0.28 (0.15, 0.53)	0.0001	8/737	0.35 (0.16, 0.75)	0.007
	Trend		0.74 (0.67, 0.82)	<0.0001		0.76 (0.66, 0.87)	<0.0001		0.72 (0.61, 0.87)	0.0004
Model 2	0–1	101/1098	1		58/1098	1		32/1098	1	
	2–3	94/1868	0.62 (0.46, 0.84)	0.0023	56/1868	0.65 (0.44, 0.97)	0.04	33/1868	0.66 (0.39, 1.13)	0.13
	4–7	20/737	0.36 (0.21, 0.62)	0.0002	11/737	0.35 (0.17, 0.73)	0.005	8/737	0.43 (0.18, 1.04)	0.06
	Trend		0.79 (0.70, 0.89)	0.0002		0.81 (0.69, 0.96)	0.012		0.75 (0.61, 0.93)	0.009
Model 3	0–1	101/1098	1		58/1098	1		32/1098	1	
	2–3	94/1868	0.53 (0.38, 0.74)	0.0002	56/1868	0.51 (0.33, 0.80)	0.003	33/1868	0.65 (0.37, 1.15)	0.14
	4–7	20/737	0.31 (0.17, 0.56)	0.0001	11/737	0.27 (0.12, 0.63)	0.002	8/737	0.41 (0.16, 1.1)	0.065
	Trend		0.75 (0.67, 0.87)	<0.0001		0.75 (0.62, 0.90)	0.002		0.76 (0.61, 0.96)	0.021

Model 1: unadjusted; Model 2: adjusted for age, sex and stratified by latitude; Model 3: as model 2 plus smoking, body mass index, education, physical activity, occupation, LDL and HDL cholesterol, triglycerides, hs-CRP, creatinine, plasma glucose, pulse pressure, antiplatelet and statin treatments.

Subgroups analysis (Fig. 1) showed that the hazard ratios (HRs) associated with one-point increase of MD score were comparable in men and women, and tended to be lower in high-risk subjects (e.g. obese, diabetics etc.) as well as in north European countries. Of note, the MD effect was comparable and statistically significant regardless of the use of statins.

4. Discussion

The high impact of MD on VEs has been previously documented [7,8,15,16] and our data are in line with these findings. We show here, for the first time, that the association of MD with VEs is more apparent in the north than in the south of Europe and is stronger in some high-risk categories, independent of statin treatments.

To the best of our knowledge, most of the studies addressing the relation between MD scores and VEs were single nation studies (Greece [7], USA [17], Italy [13], north Sweden [18]) and only one [12] was carried out in European countries at different latitudes. Our study, which includes nations with a north to south distribution, shows that latitude is the strongest predictor of the MD score. Another important observation is that MD score is associated with a high social class, as indexed by education level, and that this association is stronger in northern than in southern countries. This latter finding is not easy to explain; one of the possible explanation is that the items of MD are easily available and relatively cheap in southern Europe, whereas they are available only to higher socio-economic classes in northern countries, due to their higher cost [9,19].

Multiple complex mechanism(s) are likely to be responsible for the protective effects of MD. Indeed, MD influences both atherosclerosis and thrombosis through an effect on low-grade inflammation. In addition, several authors have reported an association between inflammatory processes and the composition of gut microbiota [20] which, in turn, has been related to dietary habits, and specifically to MD [21]. Accordingly, hs-CRP, a widely accepted marker of low-grade inflammation, has been shown to be an important mediator of the effect of MD on VEs [22].

The results of the present study are relevant in terms of public health, and fit well with current guidelines and recommendations that strongly encourage people to consume a MD-like diet for primary and secondary prevention of major chronic diseases [23]. Unfortunately, a progressive shift toward non-MD patterns is developing even in countries bordering the Mediterranean Sea [24] and this emphasizes the need for continuing the search of dietary-based preventive programs to counteract this detrimental tendency.

An important point that needs to be stressed is that our dietary assessment was based on a relatively simple dietary questionnaire, if compared with other studies [7,25], an aspect that, theoretically, could have limited our ability to detect the relevant associations. Nevertheless, the strength and consistency of our data suggest that a MD pattern can be easily extrapolated using a limited number of food items, and that its association with VEs is so strong to be detectable even in the presence of a certain degree of misclassification.

Our study has several strengths: 1) it is based on a large cohort of 3703 participants followed for more than three years by specialized clinical centers; 2) it was conducted across five European countries, with a strong gradient in latitude and incidence of VEs.

The study has also some limitations: 1) being an observational study, a causal relation between MD and VEs cannot be demonstrated; 2) as the IMPROVE participants were selected for carrying at least three VRFs, the findings can only be extrapolated cautiously to the general European population or to patients with fewer than 3 VRFs; 3) diet was assessed only at the beginning of the study and dietary changes occurring later may have led to non-differential misclassification and underestimation of the true associations.

5. Conclusions

We found that a MD score based on a simple dietary questionnaire is able to detect changes of risk of VEs; as the protective effect of MD tend to become stronger with increasing latitude. According to our findings north Europeans appear to benefit most from VE-prevention when their diet is altered to the MD diet.

Author contributions

Elena Tremoli, Damiano Baldassarre, Fabrizio Veglia, Alessandro Di Minno, Steve E. Humphries, Rainer Rauramaa, Ulf de Faire, Andries J. Smit, Philippe Giral, Sudhir Kurl and Elmo Mannarino designed research; Mauro Amato, Beatrice Frigerio, Samuela Castelnuovo, Alessio Ravani, Daniela Sansaro and Daniela Coggi conducted research; Fabrizio Veglia and Calogero C. Tedesco performed statistical analysis; Fabrizio Veglia, Damiano Baldassarre wrote the paper; Anders Hamsten, Steve E. Humphries, Rainer Rauramaa, Ulf de Faire, Andries J. Smit, Philippe Giral, Sudhir Kurl and Elmo Mannarino performed a critical revision of the manuscript for important intellectual content; Damiano Baldassarre, Fabrizio Veglia and Elena Tremoli had primary responsibility for final content. All authors read and approved the final manuscript.

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Role of the funding source

The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Declaration of interest

None.

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Appendix A. The IMPROVE study group

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