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Overall dietary variety and adherence to the Mediterranean diet show additive protective effects against coronary heart disease

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Abstract *Background and aim:* Along with the increasing evidence of the cardioprotective effects of the Mediterranean Diet (MD), the scientific interest and advocacy of dietary variety as a potentially healthy eating habit gradually faded, until its complete oblivion in the latest European cardiovascular prevention guidelines. Our study aims to investigate whether dietary variety adds to the "Mediterranean-ness" of the diet in protecting against coronary heart disease (CHD).
Methods and results: In this case–control Italian study, data on eating habits were collected from 178 patients with CHD and 155 healthy controls, primarily males, frequency matched for age and gender, using the Food Frequency Questionnaire (FFQ) of the European Prospective Investigation into Cancer and Nutrition. Adherence to MD was estimated from FFQ by the Mediterranean Diet Score (MDS), an index developed by Trichopoulou (2003) ranging from 0 to 9, with higher scores indicating a stricter adherence. Overall dietary variety was computed from FFQ as a count of single food items consumed at least once a month. Associations between MDS or overall dietary variety and coronary status were evaluated by logistic regression models adjusted for BMI, physical activity, smoking, education, and caloric intake; the Odds Ratio (OR) for CHD for each 1.5-point increase in MDS was 0.76 [IC 95% 0.59; 0.98], whereas the OR for CHD for each 15-item increase in dietary variety was 0.62 [IC 95% 0.46; 0.84]. Remarkably, adherence to MD and overall dietary variety were independently associated with a significantly reduced chance of CHD.
Conclusion: Dietary Mediterranean-ness and overall dietary variety exhibit additive cardioprotective effects.

Abbreviations: CVD, Cardiovascular Disease; MD, Mediterranean Diet; CHD, Coronary Heart Disease; CABG, Coronary Artery Bypass Graft; FFQ, Food Frequency Questionnaire; MDS, Mediterranean Diet Score.

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Introduction

The relevance of nutrition in the prevention of cardiovascular disease (CVD) is well established. Healthy eating habits have long been considered a crucial component of a heart-friendly lifestyle in CVD prevention guidelines [1,2]. The most recent European Guidelines recommend to follow the so-called Mediterranean diet (MD) [2], mainly based on a high intake of vegetables, fruits and nuts, cereals (mainly whole grains), and legumes, a moderate consumption of fish and low-fat dairy products, a preference for olive oil, a moderate intake of white meat, a low intake of red meat, and moderate daily intake of red wine during meals. The protective role of MD against CVD was initially reported in observational studies [3–7] and more recently demonstrated in a large Spanish interventional study [8]. The MD eating style has been included in the Representative List of the Intangible Cultural Heritage of Humanity [9], and it embraces a number of features that go beyond food composition, such as dietary variety, culinary tradition, conviviality during meals, and maintenance of an active lifestyle. Thus, MD is an overall lifestyle pattern, and the contribution of the individual features of MD to its efficacy in preventing CVD is not well established. Early studies showed favorable effects of dietary variety on health [10–16], although it is still debated whether this dietary feature is associated with a higher caloric intake and, consequently, with an excessive weight [17]. However, probably due to the growing evidence of the benefits of MD on cardiovascular risk factors [18] and cardiovascular events [3,4,8], the European Guidelines have gradually shifted their position from a full recommendation of dietary variety (in 2007) [1] to a mixed advocacy of dietary variety and MD (in 2012) [19], and then to an exclusive patronage of MD, without further consideration of dietary variety (in 2016) [2].

Thus, whether the extent of dietary variety adds to the “Mediterranean-ness” of the diet in protecting against Coronary Heart Disease (CHD) remains unknown. In the present study, we searched for associations between these two dietary features and CHD and their possible interaction.

Methods

Study population

This case–control study has been conducted at Centro Cardiologico Monzino, IRCCS, Milan, Italy. Overall, 333 subjects >30 and < 75 years old, living in northern Italy (93% males, mean age 62.3 ± 7.6 years) were included in the study. Patients with a diagnosis of CHD (n = 178) were identified among those admitted to our hospital for programmed Coronary Artery Bypass Graft (CABG) surgery following angiographic documentation of significant stenosis (>70%) in at least two main coronary arteries (hereinafter referred to as “cases”). Some of these cases had a remote history of CHD events or coronary interventions before enrolment (n = 97), whereas others were referred for CABG subsequently to a first diagnosis of CHD (n = 81). Controls (n = 155) were subjects without a history of any form of atherosclerotic disease recruited among the hospital staff, relatives or acquaintances, frequency matched with cases for age and gender.

Information about educational factors, smoking habits, physical activity, personal clinical history, and current drug therapies were collected from cases and controls through a structured questionnaire administered by a trained physician, who also performed a thorough physical examination and obtained anthropometric measures (blood pressure, weight, height, and waist circumference) using calibrated tools. Fasting peripheral venous blood was collected to determine serum levels of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose.

Subjects were classified in terms of smoking habits as never smokers, current smokers, and former smokers (at least 6 months of cessation). In terms of physical activity, subjects were categorized as sedentary (less than 150 min of moderate-intensity physical activity or less than 75 min of vigorous-intensity physical activity throughout the week) or active according to current guidelines [20].

Each participant provided written informed consent before enrolment in the study. The study complies with the Declaration of Helsinki and was approved by the Review Board and the Ethics Committee of Centro Cardiologico Monzino, IRCCS, Milan, Italy.

Dietary assessment

A semi-quantitative Food Frequency Questionnaire (FFQ) of the European Prospective Investigation into Cancer and Nutrition (EPIC, validated for the Italian population) [21] was administered by a trained nutritionist to collect information on food intake over the previous year. The FFQ is made up of 248 items concerning the frequency of consumption and the portion sizes of foods and beverages commonly consumed in Italy.

Completed FFQs were processed by the Epidemiology and Prevention Unit, Istituto Nazionale dei Tumori, Milan, Italy, using a dedicated software. The software calculates the frequency and amount (in grams) of foodstuffs consumed on average per day and the overall intake of nutrients and energy, using a reference database for food chemical composition.

We analysed the data obtained from FFQ to compute the Mediterranean Diet Score (MDS), a widely used index that estimates the adherence to the Greek variant of MD. MDS ranges from 0 (minimal adherence) to 9 (maximal adherence), and it is obtained by assigning 1 point when the intake of a putatively protective foodstuff is above the median or when the intake of a putatively non-protective foodstuff is below the median, and 0 points in the opposite situations. To emphasize the stringency of this score of Mediterranean-ness, the original medians of foodstuff intake determined by Trichopoulou in a Greek population, typically highly adherent to MD, were used as cut-off values [4].

Dietary variety was evaluated similarly to previous studies [22–24]. In particular, the overall variety of the diet was calculated from the FFQ as a count of all single food items consumed at least once a month. In addition, the relative contribution of variety in specific food groups to the overall dietary variety was computed by assessing dietary variety in each of the nine food groups used in MDS (18 vegetables, 3 legumes, 20 fruits and nuts, 15 cereals, 20 fish and sea food, 21 dairy products, 17 meat products, 5 animal and vegetable fats, and 5 alcoholic drinks).

Statistical methods

Continuous variables are presented as mean ± SD, and they were compared using the t-test for independent samples. Non-normally distributed continuous variables are presented as median and interquartile ranges, and they were compared using the Wilcoxon rank-sum test. Categorical data were compared using the chi-squared test or Fisher's exact test, as appropriate. The correlation between MDS and overall dietary variety was calculated by Spearman's method. The association between MDS or overall dietary variety and CHD status was assessed by logistic regression using three different models: model 1: unadjusted; model 2: adjusted for body mass index, physical activity, smoking, education, and caloric intake; model 3: model 2 + reciprocal adjustment for overall dietary variety and MDS. Due to the matching between cases and controls, no adjustment for age and gender was made. MDS and overall dietary variety were included in the models as continuous variables. In other logistic regression analyses, MDS and overall dietary variety were dichotomized as above or below their median. The results are reported as Odds Ratios (ORs) and 95% confidence interval (CI) for one standard deviation unit increase in the variables.

In order to account for a potential reverse-causality effect due to changes of dietary habits in patients because of awareness of their CHD status, we ran a sensitivity analysis by keeping in the CHD group only patients with a new diagnosis of CHD at the time of enrolment (n = 97).

To quantify the contribution of the variety within specific food groups to the overall dietary variety, we used the partial r-square in multiple regression analysis. The

Table 1 Demographic, clinical, and dietary characteristics of CHD cases and controls.

	CHD cases (n = 178)	Controls (n = 155)	p-value
Age (years)	62.8 ± 7.6	61.6 ± 7.6	0.16
Males N (%)	167 (94)	142 (92)	0.55
BMI (Kg/cm^2)	27.3 ± 3.6	26.3 ± 3.2	0.003
Waist circumference (cm)	99.6 ± 9.7	97.2 ± 9.4	0.02
Physically active N (%)	93 (52)	94 (61)	0.01
Current smokers N (%)	23 (13)	34 (22)	0.03
SBP (mmHg)	131 ± 19	136 ± 15	0.01
DBP (mmHg)	76 ± 9	83 ± 9.5	<0.0001
Total cholesterol (mg/dL)	189 ± 44	209 ± 38	<0.0001
LDL cholesterol (mg/dL)	119 ± 39	133 ± 38	0.002
HDL cholesterol (mg/dL)	45 ± 11	52 ± 15	<0.0001
Triglycerides (mg/dL)	110 (82; 147)	109 (80; 150)	0.64
Glucose (mg/dL)	121 ± 35	99 ± 14	<0.0001
Statins N (%)	109 (61)	18 (12)	<0.0001
Antihypertensive N (%)	166 (93)	67 (43)	<0.0001
Platelet aggregation inhibitors N (%)	128 (72)	14 (9)	<0.0001
Antidiabetic drugs N (%)	53 (30)	7 (4.5)	<0.0001
Years of study (years)	8 (8; 13)	13 (13; 18)	<0.0001
Food intake:			
Vegetables (g/day)	163.4 (114; 237)	163.1 (119; 240)	0.78
Legumes (g/day)	8.85 (3.5; 18)	9.8 (4.6; 18)	0.42
Fruits and nuts (g/day)	297.15 (220; 402)	282.4 (182; 387)	0.30
Cereals (g/day)	233.95 (170; 300)	241.3 (192.4; 290.6)	0.58
Fish and seafood (g/day)	30.25 (16; 50)	34.8 (22; 57)	0.01
Meat and meat products (g/day)	112.05 (88; 148)	109.8 (81; 154)	0.76
Dairy products (g/day)	79 (47; 130)	86.3 (43; 140)	0.72
Fats: butter (g/day)	1.8 (1.6; 1.9)	1.5 (1.3; 1.6)	0.005
Fats: olive oil (ml/day)	21.1 (19; 23)	22.1 (20.0; 25)	0.45
Red wine (g/day)	63.5 (0; 222.2)	111.1 (8.9; 222.2)	0.19
Ethanol (g/day)	12.17 (1.6; 26.62)	13.80 (4.32; 31,08)	0.07
Energy (Kcal/day)	2213 (1766; 2650)	2198 (1818; 2667)	0.22
MDS (points)	4.2 ± 1.5	4.7 ± 1.3	0.001
Overall dietary variety (points)	68 ± 14	75 ± 15	<0.0001

The continuous variables are presented as mean ± standard deviation, and they were compared using the t-test for independent samples; non-normally distributed variables are presented as median and (interquartile ranges), and they were compared using the Wilcoxon rank-sum test; categorical data are presented as frequency and (percentage).
BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; MDS: Mediterranean Diet Score.

variety within each food group was normalized as the actual number of food items consumed divided by the total number of items included in the group. P values < 0.05 were considered as significant. All analyses were performed using SAS v.9.4 (SAS Institute Inc. Cary, NC, USA).

Results

Table 1 summarizes the clinical characteristics of the participants, stratified by CHD status.

Due to the matching, age and sex were comparable between groups. As expected, CHD patients differed significantly from controls in many clinical variables, including prevalence of traditional risk factors and use of one or more drugs for secondary prevention. Table 1 also shows the intake of the nine food groups of MDS as well as the energy intake, the MDS score and the overall dietary variety score in cases and controls. Cases consumed significantly more butter and less fish/seafood than controls. Energy intake was similar between the groups. MDS and overall dietary variety were significantly lower in cases than in controls. The mean difference in MDS was only about 0.5 points, but the strong statistical significance indicates that controls systematically adhered more strictly to MD.

In addition, the intake of food items in cases with a remote history of CHD events was not significantly different to that of cases referred for CABG subsequently to a new diagnosis of CHD, except for a higher intake of red wine ($p = 0.0045$) and ethanol ($p = 0.0006$) and a reduced intake of dairy products ($p = 0.009$) in the former group (data not shown).

MDS and overall dietary variety were significantly, but weakly, correlated ($r = 0.15$, $p = 0.006$).

Results from logistic regression analyses showed that both MDS and overall dietary variety were significantly associated with a reduced risk of CHD (Table 2). In particular, after full adjustment (Table 2, model 3), a standard deviation increase in MDS (1.5 points) was associated with a 24% reduction of CHD risk, and a standard deviation increase in overall dietary variety (15 items) was associated with a 38% reduction of CHD risk.

Notably, in model 3, both MDS and overall dietary variety were significantly associated with CHD risk reduction, indicating that each dietary feature is independently associated with CHD status. No significant interaction ($p = 0.13$) between MDS and overall dietary variety was detected. The combined effect of adherence to MD and overall dietary variety on CHD risk is shown in Fig. 1. Compared to subjects with both MDS and overall dietary variety below the median, the group with both MDS and overall dietary variety above the median showed a 70% reduction of CHD risk (OR = 0.30, 95% IC: 0.15–0.62).

In a sensitivity analysis including only cases with a new diagnosis of CHD, results were similar to the main analysis (data not shown).

As shown in Fig. 2, within major food groups, variety in vegetables was the most important contributor (partial r-square = 0.23) to the overall dietary variety, followed by the variety in the group of fruits and nuts (partial r-square = 0.14).

Discussion

The association between food habits and cardiovascular disease is known. Several investigations have reported inverse relations between MD and risk of cardiovascular disease. Previous observations from cohort [3–7] and case–control studies [25–27] were reinforced by the results of a recent randomized controlled trial [8] in high-risk subjects, showing that adherence to MD significantly

Table 2 Association between Mediterranean Diet Score (MDS) or overall dietary variety and coronary heart disease.

	MDS	p-value	Overall dietary variety	p-value
Model 1	0.71 (0.56; 0.88)	0.003	0.59 (0.47; 0.75)	<0.0001
Model 2	0.76 (0.59; 0.97)	0.03	0.61 (0.45; 0.83)	0.002
Model 3	0.76 (0.59; 0.98)[a]	0.04	0.62 (0.46; 0.84)[b]	0.002

Results were assessed by logistic regression and are expressed as standardized odds ratio, for a one standard deviation increase in Mediterranean diet score or overall dietary variety (confidence interval 95%). Model 1: Unadjusted; Model 2: Adjusted for BMI, physical activity, smoke, years of study, and caloric intake; Model 3: Model 2 + reciprocal adjustment for

[a] Overall dietary variety;

[b] Mediterranean Diet Score.

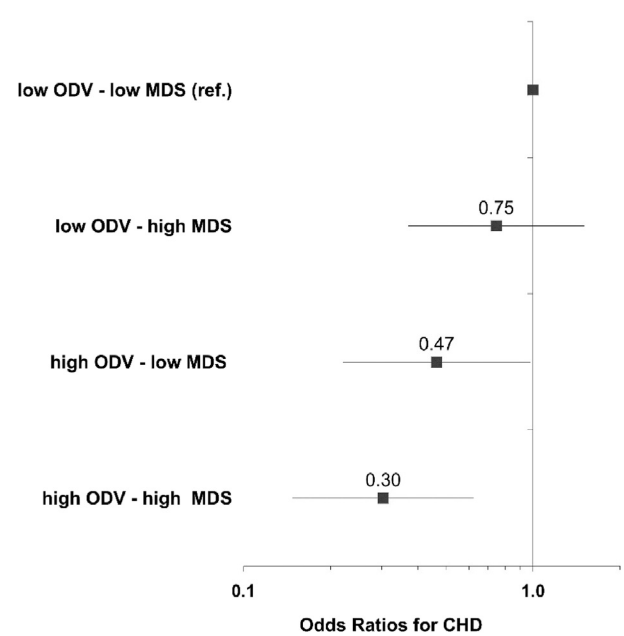

Figure 1 Relationship between adherence to the Mediterranean diet, extent of overall dietary variety, and coronary heart disease. Odds Ratios for coronary heart disease adjusted with Model 2 (BMI, physical activity, smoke, years of study, and caloric intake) by categories of Mediterranean Diet Score (MDS) and overall dietary variety (ODV). For both variables, low: < median; high: > median.

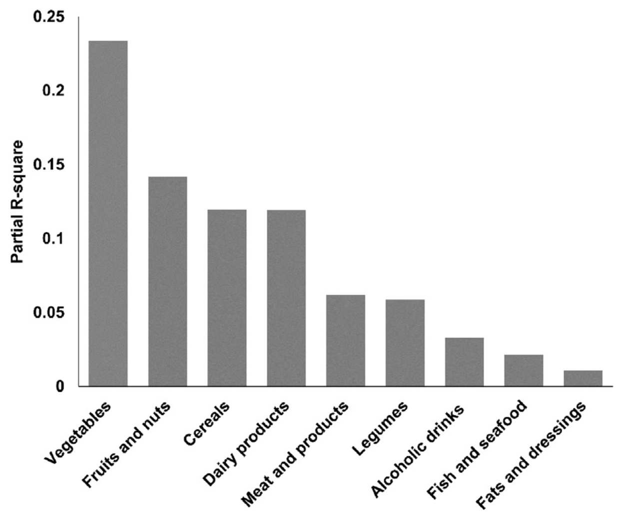

Figure 2 Proportion of the variance of overall dietary variety explained by variety in different food groups. The proportion of the variance of overall dietary variety explained by the variety within different food groups is quantified by partial r-square in multiple regression analysis. The variety within each food group is normalized as the actual number of food items consumed divided by the total number of items included in the group.

lowers the risk of cardiovascular events. In the present study, the mean absolute difference in MDS between cases and controls was rather small (0.5 points). However, as indicated by the OR, just a 1.5-point increase of the score is associated with a nearly one-quarter reduction in CHD risk. The results of the present Italian case–control study are in line with these previous data. It is worth noting that, in our study, the association between MDS and CHD may have been particularly evident since we used, as cut-off values to compute individual MDS, the median intake of food items reported in a Greek population, typically highly adherent to MD. Indeed, in an exploratory analysis using as cut-off values the median intake of food items of our own sample, as some authors did [28,29], the association between MDS and CHD did not reach statistical significance (data not shown). These data suggest that, to prevent CHD, being just more adherent to MD than the average of one's own population is not enough, but a stricter respect of the traditional MD is needed. Besides, these data suggest that the use of proper cut-off values in estimating individual MDS is crucial to uncover associations between MD adherence and health status, especially in populations who do not usually follow a stringent MD. MDS was positively, but weakly, correlated with the overall dietary variety, which is consistent with the understanding that, among its features, dietary Mediterranean-ness comprises varied food choices. Adopting a varied diet has long been a generic and widespread nutritional advice, though the scientific evidence available so far on the benefits of dietary variety for health is limited, and in some cases inconsistent. In particular, the studies on dietary variety have reported heterogeneous associations with obesity [17,30,31] (in this study, no association between dietary variety and BMI was observed) and the measures of variety differed highly between studies [22,24,31,32]. Moreover, most previous data about dietary variety and health refer to associations with some cardiovascular risk factors [10,14,15,33] or frailty [12,34]. As far as we know, only one study evaluated the associations between dietary variety and CHD, and the results were not significant [35]. However, only variety in fruits and vegetables was considered in the cited study. We also observed an inverse association between variety in fruits and vegetables and CHD status, but it did not reach statistical significance. Instead, the *overall* dietary variety was an independent predictor of CHD status. This finding suggests that variety in foodstuffs other than fruits and vegetables, which accounts for 63% of the overall dietary variety, may add significant protection against CHD. Therefore, our data suggest that, to achieve the highest cardioprotective potential of the diet, a high variety of fruits and vegetables from different sources, as advocated by recognized scientific societies [36–38], should be integrated with a high variety of other food classes. This collides with some current opinions that propose to cut out whole food groups or macronutrients (dairy products, meat, carbohydrates, etc.) to maintain or improve health.

Finally, we believe that a relevant finding of our work is that, as illustrated in Fig. 1, adherence to MD and overall dietary variety are additively associated with protection against CHD. Therefore, dietary variety may maximize the efficacy of MD, beyond the potential beneficial effects on cardiovascular health of specific functional foodstuffs that make up MD, such as fish [39], olive oil [40–42], red wine [43], and nuts [44,45].

Although interventional studies are necessary to corroborate the cardioprotective contribution of overall dietary variety to a high MD adherence, the presented data suggest considering the reintroduction of a varied food choice, maintaining an adequate caloric intake, among the recommendations for cardiovascular prevention, in addition to the adoption of a Mediterranean dietary style.

The present study has some limitations. First, it is an observational study, thus an influence of residual unknown confounding factors may not be excluded. Second, it is a retrospective case–control study, thus it is not possible to determine whether the observed associations between dietary features and CHD are cause-effect or are related to dietary choices in patients long aware of their CHD status (reverse causality). Yet, dietary features were similar in patients with a long history of CHD and in those with a new diagnosis, and the main results were unchanged after excluding the former group of patients from the analysis. Third, given the large prevalence of males in our study, which is typical of cohorts of patients undergoing CABG, we do not know whether the results apply to females.

Conclusions

In conclusion, this case–control Italian study corroborates the beneficial association between adherence to MD and CHD status, it reveals a protective association between overall dietary variety and CHD status, and it shows an independent and additive cardioprotective effect of the two dietary features. These results, if confirmed in larger studies, call upon the reintroduction of a varied food choice in the nutritional recommendations for cardiovascular prevention, beyond the adoption of a Mediterranean dietary style.

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Declaration of Competing Interest

The authors have nothing to disclose.

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